Pathogenic Organisms – Toxic Mechanisms

Name	Toxin Type	Mechanism	Molecular Result	Clinical Result
Corynebacterium diphtheriae	Diptheria Toxin	Inactivate EF-2 via ADP ribosyltransferases	Inhibit protein syn	Upper resp tract infection, sore throat, low fever
Pseudomonas aeruginosa	Exotoxin A	Inactivate EF-2 via ADP ribosyltransferases	Inhibit protein syn	UTI
Shigella dysenteriae	Shiga Toxin	Inactivate 60S ribosome via RNA N-glycosidase	Inhibit protein syn	Abdominal pain, fever. Low V, bloody, mucoid, hi WBC stools. HUS, Reiter's SX. Toxin binds to Gb3 receptor on glomerular epi cells. Swelling and fibrin deposits in glomerulus. Travel via marcos
Escherichia. coli	Shiga Toxin	Inactivate 60S ribosome via RNA N-glycosidase	Inhibit protein syn	
	Heat-labile (LT) enterotoxin	Activate adenylate cyclase via ADP ribosylation of Gs	Activate 2nd messenger path	Increase cAMP, secretory diarrhea
	Heat-stable (ST) enterotoxin	Activates guanylate cyclase	Activate 2nd messenger path	Increased cGMP, secretory diarrhea
Vibrio cholerae	Cholera Toxin - Heat-labile (LT) enterotoxin	Activate adenylate cyclase via ADP ribosylation of Gs	Activate 2nd messenger path. Inc CL- out and Dec Na in	Increase cAMP, Hyper secretory diarrhea of fluid and electrolytes.
Bordetella Pertussis	Pertussis Toxin	Activate adenylate cyclase via ADP ribosylation of Gi	Activate 2nd messenger path.	Increase cAMP, secretion in URT & other tissue effects
Clostridium tetanus	Tetanus Toxin	Blocks release of glycine from inhibitory neurons.	Zinc-dependant proteases cleave VAMP	Uncontrolled muscle spasms
Clostridium botulinum	Botulinum Toxin (A,B,E)	Blocks release of acetylcholine at N-M juncts	Zinc-dependant proteases cleave VAMP	Flaccid paralysis
Bacillus anthracis	Anthrax Toxin	Protect Ag, Edema, Lethal		

Super Antigens – Expands T-Cells and Cytokine release

1) TSST-1
2) Group A Strep
3) Toxic-like TSST-1

Bacteremia is caused by gram negative endotoxin release (LPS)

Pathogenic Organisms – Enterobacteriaceae – Lower GI

Name	Clinical	Pathogenesis	Pathogenesis	Virulence	Other
Shigella spp – Gram neg rod, **non-motile**, no lactose, **H2S neg**, close rel E. Coli, fecal/oral route, high contagious via low dose, human specific, oxidase negative					
S. Dysenteriae – Grp A Rare – most severe S. Flexneri – Grp B 3rd World S. Boydii – Grp C Rare S. Sonnei – Grp D US – food handlers (Phage acq shiga toxin)	**Shigellosis, Bacillary or Colonic Dysentery** – Abdominal pain, fever. Low V, bloody, mucoid, hi WBC stools. HUS, Reiter's SX. Cannot ferm lactose, sucrose or xylose	Through stomach – low dose infectious, Transient mult in SI – watery diarrhea, Stop in Colon, thru M-cells into epi basolat. Apoptosis of macros. Mult w/in cyto of epi cells	Cell-Cell spread via actin tail form'n. Intense, acute inflamm and mucosa destruct – causes ulcers/abscess. Rarely into blood.	Large virulent plasmid for invasion and spread, Ipa proteins. Shiga Toxin in Dysenteriae inhibits protein syn on chromosome	1-4 y/o kids, day-care centers. Stool culture, fecal smear for polys, self-limiting, GI motility OK Non-invasive 30C, invasive 37C
Salmonella spp – Facultative gram neg rods, **motile**, no lactose, **H2S pos**, motile, fecal/oral route, oxidase negative					
S. enterica (**typhoid fever**) S. paratyphi (A,B,C) (**paratyphoid fever**)	Fever, malaise,myalgia, bloody diarrhea, Rose spots. 3-4 wks untreated.	Infection w/human feces. Adhere to M-cells. Invade macros, spread via blood to liver/spleen via LNs	Myocarditis, liver, bone damage, intestinal perf, local infect away from GI. Chronic asx carriers.	No plasmid, Vi capsule – inhibits complement killing. Treat with xbios.	Diag- blood/stool cultures, Ig's to Vi Ag protective. Human reservoir. Wait in gall stones
S. enteritidis, S. typhimurium – **enterocolitis** 1st world	Diarrhea, modest WBC, blood in stool. 7-days self limiting	Infection w/animal feces, colonize in SI.	Epi cells in ileum, colon, mult w/in vacuole. No necrosis.	Large plasmid, Treat with fluids and electrolyte	Animal reservoir. Eggs/reptiles. Large scale food product
S.typhimurim, S. cholerae-suis – (**septicemia**)	W or w/o focal lesions in lungs, bones, meninges. Fever, chills, anorexia (cancer).	Pre -anemia – sickle osteomylitis. Pre-CV-endocarditis AIDS hi risk.	Salmonella inside invading Schistosoma mansoni – chronic systemic infection.	Large plasmid	

Name	Clinical	Pathogenesis	Pathogenesis	Virulence	Other
Yersinia sp. – Facultative gram neg rods, no lactose, motile only at 25C, optimal growth at 22-25C, **Not at 37C,** also cause xtraintestinal infections, primarily animal pathogens.					
Y. enterocolitica, (**enterocolitis**) O3, O8, O9 serotypes	Fever, diarrhea, abdom pain, stool WBC/blood Reiter's -HLA-B27. Diarrhea from endotoxin or invasion	Animal feces in milk/water. Penetrate epi cells of Peyer's Patches. Mult w/in macros.	No treatment except for septicemia.	Heat-stable toxin, chromosome-**invasins**, plasmid-outer mem proteins	Distant geograph distribution of serotypes for Y. enterocolitica
Y. enterocolitica, Y. pseudotuberculosis (**mesen-lymphitis**) O1 serotype	Fever, LRQ abdom pain, mimic appendix. Enlarged mesenteric lymph nodes.	Animal feces in milk/water. Penetrate epi cells of ileum to lymph nodes.	No treatment except for septicemia.	Chromosome-**invasins**, plasmid-outer mem proteins	No Vaccine
Escherichia coli – Faculative gram neg rods, ferm lactose, normal commensals (opportunistic) & frank pathogens. Intestinal and extra-intestinal, oxidase negative					
Diarrheagenic E. Coli					
Enterotoxigen –ETEC **Traveler's/children's diarrhea**	Acute secretory diarrhea. **No Blood or PMNs**	Human feces, Adhere to SI epi cells via CF. Syn LT or ST toxin. No invasion.	**LT** similar to cholera. Activates adenylate cyclase – inc cAMP. **ST**- activates guanylate cyclase – inc cGMP.	**LT/CF** plasmid, **ST** transposon on plasmid	Underlying immunity in adults. No vaccine – high # of serotypes and diff CF antigens
Enteroinvasive – EIEC **Bacillary dynsentery** (no ferm lactose)	Identical to shihellosis - Abdominal pain, fever. Low V, bloody, mucoid, hi WBC stools. HUS, Reiter's SX **Blood and PMNs**	Through stomach – low dose infectious, Transient mult in SI – watery diarrhea, Stop in Colon, thru M-cells into epi basolat. Apoptosis of macros. Mult w/in cyto of epi cells	Cell-Cell spread via actin tail form'n. Intense, acute inflamm and mucosa destruct – causes ulcers/abscess. Rarely into blood.	Carry invasion plasmid of Shigella	Human specific
Enteropath – EPEC **Infant diarrhea**	Acute and chronic, watery diarrhea. **No blood or PMNs**	**A/E Lesions** on SI brush border. Must have intimin to form A/E lesion.	Malabsorption or signal transduction cause of diarrhea. Chromosome PAI encodes **Intimin** and proteins.	**Bundle-forming pilus** on plasmid **Intimin** (A/E lesion) and proteins for signal trans.	Kids <2y/o Rarely Adults Nurseries/day care No vaccine – breast feed protect

Shiga-toxin - STEC Enterohemorr – EHEC **Hemorrhagic colitis and HUS** (No ferm sorbitol therefore screen w/SMAC)	Copious, bloody diarrhea in HC with abdominal pain. No fever, non-invasive. HUS – micro hemolytic anemia, thrombocytopenia, glomerular thrombosis **Blood and PMNs**	**A/E lesions** on epi cells in colon for EHEC. **Low infectious dose – 2nd spread is common.** **5-10% of shiga toxin HC go to HUS**	PAI encodes **Intimin** and proteins for EHEC. STEC no PAI therefore no A/E lesions. **Xbios may increase severity of HUS by inducing prophage.**	Bacteriophage encoded Shiga toxin – entero and cyto toxin. Worse diarrhea and HUS. Shiga toxin on Gb3 receptor on glomerular endothelium cells	Emerging infectious agent. EHEC O157:H7 major serotype in US. Animal feces in food/water.
Enteroaggreg – EAEC **Infant diarrhea** (developing countries)	Acute and persistent diarrhea in infants **No Blood and PMNs**			**CF and ST**	O157:H7 no sorbitol, screen with MacConkey SMAC
Name	Clinical	Pathogenesis	Pathogenesis	Virulence	Other
Vibrionaceae – Comma-shaped Gram neg rods, glucose ferms, oxidase pos, polar flagella, motile, abundant in marine and surf water					
V. Cholerae O1/O139 **Epidemic/Pandemic Cholera**	Acute diarrhea from toxin. No invasion. Asx or cholera gravis. Nausea, vomit, copious watery diarrhea with abdominal pain. No fever. **No Blood and PMNs**	Rice water stools, rapid fluid and electro loss. Hypotensive, poss shock. Attach to brush border epi cells via Tcp pilli – colonize.	Toxin causes fluid secretion. Feces in water. Hi dose req. Only human host. Mostly in kids 2-9, adults develop immunity.	LT – bacteriophage Tcp pilli receptor 5B & 1A subunits. B-GM1 ganglioside A-act adenylate cyclase	Classical and El Tor for O1, O139 identical to El Tor except for O-Ag and polysaccharide capsule
V. Cholerae non-O1 **Diarrhea – most Asx**	Diarrhea w/o Cholera Toxin. 1-4 incubate	Kids 2-9y/o hi risk in endemic areas	Treat via ORT, fluids and electros. Poss tetracycline.	PCR/DNA for CT gene	Only human hosts. Diag via agglut with Ig against O1 or O139
V. parahaemolyticus **Acute water diarrhea, sometimes bloody**	Abdominal pain, vomit, 15 hour incubate	Toxinogenic Mech ??		Kanagawa Toxin (hemolysin)	Undercooked or raw seafood. Japan.
V. Vulnificus **Wound infect, gastroenteritis, septicemia**		**Risk for septicemia** – liver disease, iron-overload disorders, diabetes, AIDS or malignancy	Exposure to contam sea water for wounds. Eating raw oysters for septicemia.		

Name	Clinical	Pathogenesis	Pathogenesis	Virulence	Other
Campylobacter Jejuni – comma shaped (gull, S) rod, gram neg, slow growing, motile, oxidase pos, microaerophilic, urease neg, special culture for diag with xbio, high CO2, 42C.					
C. Jejuni Enteritis Colitus	Fever, abdominal pain, diarrhea. Stools similar to Shigella. Self-limiting	Adhere to upper SI, mult, invasion, inflamm. Eventually to colon – Colitis.	Animal feces in food/water. Diag via oxidase pos, clear/grey colonies	Treat with fluid/electrolytes, poss Erythromicin.	Most frequent cause of diarrhea in US. Undercooked chicken. 40% of GBS had C. Jejuni infection.
C. Jejuni Reiter's Sx	Post-infection reactive arthritis in HLA-27 pts				
C. Jejuni Guillain Barre Sx	Demyelination – acute neuro-musc paralysis. 3 wks after infect	Lipooligosacc mimics human gangliosides therefore autoimm rxn			
Helicobacter pylori – Spiral-shaped, miroaerophilic, motile, urease pos (allow bugs to survive low pH)					
H. pyl;ori Chronic gastritis, duodenal/peptic ulcers Gastric carcinoma	90% Peptic ulcer disease caused by H. Pylori. May protect from gas reflux dx and adenocarcinomas of lwr esophagus & cardiac part of stomach.	Oral ingest via feces, dental plaque and gastric contents. Penetrate mucus and colonzie gastric epi. Invasion, toxins and urease damage epi	Inflamm response, vacuolation of epi cells then destruction, syn ulcer. Treat w/ amoxicillin and metronidazole and omeprazole for 14 days H2 receptor agaonists is very expensive and lifetime use.	Urease – urea to NH4, epi cell damg Flagella – swim against peristalsis VacA- damage epi Mucinase, phospholipases – disrupt mucus SOD/Catalase block poly toxic O2 radicals CagA – on PAI	Uncommon mixed strain infections. Diag – Culture or urease activity "Breath Test" (radiolabled CO2), plasma or salivary IgG/IgA response.
Pseudomonadaceae – Aerobic, gram neg rods, oxidize glucose (no ferm), polar flagellum, **opportunistic, Non-diarrheal,** grows at 37-42C					
P. aeruginosa **Local infection** – Eyes, ears, burn wounds, dermatitis, UTI	Invade deep w/in tissue	Extracell proteases & Hemolysin (destroy tissue/invasion), Endotoxin (LPS), Flagella and twitching motility, form biofilm	Exotoxin A – inhibit protein syn, ident to Diphtheria toxin Exotoxin S – inhibit protein syn via ADP-ribosylation	Pili – adherence, Alginate capsule, pyocyanin – impairs ciliary act	Grape odor/ bright green pigment (pyoverdin) **Deadly systemic dx in burn pts, cystic fibrosis.**
P. aeruginosa **Systemic infection** – CF (lungs), sepsis	LPS – fatal sepsis	Avoid single-drug therapy, hi resistance capability.		Feces and soil	Opportunistic, but virulent when estab

Extraintestinal Enteric Bacterial Infections

UTI

1) Ascending – most common – from periurethral to bladder (cystitis) and/or to kidneys (pyelonephritis)
2) Hematogenous – less common – to kidney from bloodstream
3) Uncomplicated - Treat with SMZ/TMP (80% E. coli)
4) Complicated – catheterized, immune surpressed, anatomical defects. Many agents, xbio not always works, relapse
5) 80% E. Coli UPEC - P fimbriae adhesins and hemolysin on chromosomal PAI, Type I fimbriae for colonization/exfoliation of bladder cells
6) Proteus mirabilis – swarming motility, upper UTI, kidney stones (urease)
7) Gram neg rods - P. aeruginosa, Enterobacter sp., Klebsiella pneuomoniae cause complicated UTI

Neonatal Meningitis

1) E. Coli K1 – K1 ag - <4wks old
2) Citrobacter freundii – uncommon, brain abscesses

Primary Lobar Pneumonia

1) K. pneumoniae – urease, lactose ferm, non-motile, encapsulated (phago protection), 3% all pneumoniae
2) Other Klebisella sp. and other Enterobacter sp.

Wound Infection

1) Gram neg enteric bacteria – Klebsiella pneumonia, Proteus sp., P. aerginosa

Bacteremia, Endocarditis

1) E. coli
2) Other gram neg enteric bacteria

Septicemia

1) Sepsis – harmful host response to infection – resp/renal failure, coag abnormal, hypotension
2) Sepsis – Chills, fever response to endotoxin – lipid A of LPS, continuous (blood site) and intermittent (distal site) septicemia
3) General Sepsis –Enterobacter sp. encapsulated lactose ferm, often in parenteral fluids
4) General Sepsis – Serratia marcescens – syn red pigment, slow lactose ferm, motile, likes glucose, in parenteral fluids
5) Transfusion Sepsis – Yersinia enterocolitica, Salmonella sp., Campylobacter sp.
6) Septic Shock – In response to **endotoxin (LPS) induced release of TNF-alpha** – vasodilation, fluid leak into tissues, DIC, low clotting proteins, hypotension, wasting and organ failure.

Intestinal Parasites

Name	Clinical	Pathogenesis	Pathogenesis	Virulence	Other
Intestinal Protozoan					
Entamoeba Histolytica – WW, fecal/oral, trophs and cysts	**Invasive amebiasis** – profuse bloody diarrhea/dysentery, fever. Recurrence rare.	Impaired immune response b/c of phago of macros and polys. **Trophs must adhere to kill**	Spread via blood to liver – hepatic abscess.	Galactose adher protein Amoebapore Surf cysteine proteases Phagocytic Diag via trophs/cysts in stool	Amebic ulcers. Amebomas – 1%. Bleed into gut. **Serum IgA and IgG if invasive**
Giardia Lamblia WW, fecal/oral, trophs and cysts	Asx to chronic diarrhea, Poss **explosive, watery, foul diarrhea, cramps, light fatty stools**.	Trophs adhere to upper SI – facultative anaerobes. Mild damage to villi – malabsorp sx	IgA, T-cells and macros.	Diag via cysts/trophs in stool	Recurrence poss, some immunity.
Cryptosporidium parvum – Zoonosis, fecal/oral, small dose	Asx to profuse watery diarrhea, nausea, fever, self-lim	**Intracellular enterocyte cytoplasm facing lumen**, BB. CMI host response	CMI role (Th1), IgA from breast milk	Diag via oocysts in feces, no drugs available.	Oocytes very resistant. **Internal autoinfection.** Much worse if AIDS
Helminth Infections – unlike bacteria and protozoa, adult worms do not mult in intestine					
Hookworms A. Duodenale N. Americanus Eggs in feces, filariform larve in soil	Abdominal pain, diarrhea, black stools, eosinophilia. **Iron defic anemia.** Pica, allergic rxn	Attach and feed on GI mucosa (villi). **Blood and fluid loss.**	Live 5-7 yrs	Anticoag, Acetylcholinesterase Hyaluronidase	Diag – eggs in feces
Trichuris Trichiura (whipworm) Eggs in feces, embryo in soil	Most infections light. Heavy infect – malnutrition, chronic dysentery, colitis	Embed perm in LI mucosa. Low blood loss	Live 4-8 yrs	Diag via eggs in feces	Prolapse rectum if severe
Ascaris Lumbricoides Eggs in feces, adults in SI.	Protein/energy malnutrition	Large worms compete w/host for food. Damage from size.	Hypersen rxn to lung migration. Live about 1yr	With agitation may perf GI. Many cause obstruction.	Eggs highly resistant. Diag – eggs in feces, larvae in sputum

Name	Clinical	Pathogenesis	Pathogenesis	Virulence	Other
Strongyloides stercoralis Rhabditiform larvae in feces, filariform larvae penetrate skin	Malabsorption Sx, Asx to life-threaten, Diarrhea, pain, bleeding, black stools, anemia	Invade GI mucosa. Larvae currens- allergic inflam rxn in skin and lungs	Live >50 years	**Internal Autoinfection.** Diag via rhabditiform larvae in feces	AIDS – accelerate larval development. No shoes. Larval currens. Loeffler's pneumonitis.
Enterobius Vermicularis (pinworm)	Pruritis ani	Adults in cecum, eggs deposit in perianal skin	Reinfection common	Diag – via eggs on perianal skin	Most common in US/Europe. Resistant eggs.
Taenia Solium (pork tapeworm) Scolex and proglottids	Usually Asx to cysticerci larvae in CNS. Space occupying lesion.	Ingest raw pork. **Larvae cysticercus causes cysticercosis in CNS**	Live for decades	Scolex and proglottids in feces	T. Saginata (beef tapeworm) not as dangerous – no cysticercosis
Diphyllobothrium latum (fish tapeworm)	Usually Asx, abdominal pain, diarrhea, weight loss	**Attach in ileum, compete for B-12**	Live for decades		Poss reduced folate absorption
Fasciola Hepatica (sheep liver fluke)	Abdominal pain, hepatomeg, jaundice, fever, diarrhea	Damage and irritation to liver during migration.	Mechanical obstruction, toxic waste	Diag via eggs in feces	Biliary dilation/obstruction.
Clonorchis Sinensis (Chinese liver fluke)	Asx for light, to biliary obstruction, diarrhea, pain, enlarged liver, jaundice	Thickening and dilation of bile ducts with hyperplasia of bile duct mucosa	Live >50 years	Diag via eggs in feces	Small bile ducts.
Fasciolopsis buskii (giant SI fluke)	Asx for light to pain, diarrhea, obstruct, malabsorption, ulcer			Diag via eggs in feces	

Anaerobes – No catalase or Superoxide dismutase, all gram pos except bacteroides fragilis (gram neg)

Name	Clinical	Pathogenesis	Pathogenesis	Virulence	Other
Clostridium botulinum (botulism from food, wounds or infant GI)	12-36h after ingest, dry mouth, dysphagia, double-vision, descending paralysis. No fever.	Toxin release during growth and autolysis. Toxin A,B and E	Treat with anti-toxin.		Stops acetylcholine release at N-M juncts and cleaves VAMP. **Spores in soil.**
Clostridium tetani (tetanus spores enter from injury to skin)	Local spasm may precede generalized. Trismus, risus sardonicus, rigid musc. Block normal resp.	Toxin released when cells lysed. Spread via blood/lymph	Diag: Toxin present from cultured wounds.	Treat with anti-toxin, penicillin. Immunize.	Gram pos rod, soil and feces of animals. Cleaves VAMP, stops glycine from inhibitory neurons.
Clostridium perfringens	Invasive Infections and Intestinal disorders. Self limiting in GI.	Alpha toxin – lecithinase causes hemolytic, platelet damage.	Much milder and no neuro sx compared with Botulism GI dx.	Toxins in tissues plus enterotoxin	Gram pos rod, aerotolerant in milk
Clostridium Difficile (pseudomem enterocolitis)	Necrotize Colon, form pseudo membranes. Profuse watery diarrhea, cramps, green mucoid stools.	Overgrows normal gut flora during xbio treatment.	**Hospital acquired after xbio treatment**	Toxins A&B (cytotoxin and enterotoxin)	Gram pos rod. Spores resist staining
Bacteroides fragilis	Tissue destruct and resulting abscess formation	**Highest virulent anaerobe.**	Normal flora of URT, GI, Female GU.	Polysacc capsule. Resists penicillin	Obligate anaerobe, no spores, non-motile, gram neg

Useful Gram Stain

1) Lower respiratory tract – not URT
2) Genital – not GI or Urinary
3) Skin/Wound
4) Deep Tissue
5) Sterile fluids – but not blood (too dilute)
6)Anaerobic Infections
7) CSF

Bascillus Infections – Gram pos spore forming rods, most opportunistic, anerobic, primarily an acute disease of herbivores. Dx often with wool shearers cutaneous and inhalational.

Name	Clinical	Pathogenesis	Pathogenesis	Virulence	Other
Bacillus cereus Food poisoning Ocular infections Catheter sepsis	Diarrhea after ingestion. Infection in eye after trauma with soiled object IV catheter-related sepsis				
Bacillus anthracis (anthrax) Cutaneous, GI and Inhalational	Skin – **Eschar** - black, deep, necrotic, edema, no pus, many bugs in eschar aspirate. GI – massive ascites, pain, bloody diarrhea. Inhale – Hemorrhagic **mediastinitis**, cyanosis	EF + PA = edema LF + PA = death Humans from hides, hair, wool or bones	Produce anti-phago D-glutamic acid capsule	EF- Edema factor LF – Lethal factor – inhibits NAPK signal path in macros PA – Protect Ag	Aerobic, **spore forming**, gram pos rod. In soil. Cutaneous dx is 95% of human cases. Vaccine – no live component

Community acquired Bloody Diarrhea

1) Campylobacter Jejuni
2) EHEC
3) STEC
4) EIHC
5) Shigella
6) Salmonella
7) Yershinia Enterocolitica

Serotyping

1) H Antigen - Flagella
2) O Antigen – Term polysac of LPS
3) K Antigen - Capsule

Reiter's Syndrome – Campylobacter, Salmonella, Y. Enterocolitica

1) Aseptic poly arthritis
2) Link to HLA-B27
3) Days to months after diarrhea
4) Uveitis
5) Painful urination

Otitus Media Causes

1) H. Influenza nontypeable
2) Strep Pneumoniae
3) P. Aeruginosa
4) Moraxella Catarrhalis
5) Proteus

Name	Clinical	Pathogenesis	Virulence	Other
Staphylococcal spp. – Gram pos cocci in clusters, facultatively anaerobic, non-motile, non-spore form, **catalase pos,** quick xbio resistant, suppuration, necrosis and abscess formation, blood agar with mannitol salt				
S. Aureus Skin Infections	Furnucle(boil), stye, acne, Carbuncles(subcut abscess), Impetigo(large acute cutaneous lesions)		**Surf components:** 1) Gram pos PG – septic shock 2) PG w/ ribitol-techoic acid 3) Protein A – binds Fc portion of IgG, antiphago activity 4) Capsule – x-phago 5) Clump factor – binds fibronogen 6) Coagulase – convert fibrinogen to fibrin, coat self with fibrin,anti-phago **Xcell Bact products:** 1) Coagulase – wall off 2) Alpha hemolysin – Lyse RBC,WBC,platelets via xmem pores 3) **PVL – kill PMN/macro via mem pore. Poor prognosis.** 4) Exfoliatin – scaled skin sx LT and/or ST- cut desmosome link 5) Hyaluronidase – hydros hyaluronic acid – helps bug xport 6) Enterotoxin (ABCDE) – food poisoning – good after 30 min of boil 7) TSST-1- pyrogenic and super Ag, cyto release, cap leak, hypotension and shock.	**Coag positive,** Bullus Impetigo highly contagious. Poor hygine.
S. Aureus Wound Infections	Suppuration hallmark – pus filled local abscess.	Autoinoculation, med personal, IV lines		**High risk in wet conditions**
S. Aureus Deep Lesions – very serious	Osteomyelitis, septic arthritis,endocarditis, septicemia, meningitis	Immunecomprised increased risk (low granulocytes), IV drug users		Most staph penicllin resistant, use methicllin or vancomycin
S. Aureas Pneumonia – very serious	Secondary to trauma and influenza. CF at high risk.			Beta hemolytic = yellow.
S. Aureas Food Poisoning	Acute vomiting and diarrhea 1-5 hrs, no fever	Pre-formed ST enterotoxin mediate		Potato salad, creamy dishes, self limited
S. Aureas Scalded Skin Sx	Erythema, bullous form, **desquam epi cells (sheets)**	**Exfoliation** in infected lesion. Spread in blood.		**Children under 5. Toxin mediated.**
S. Aureas Toxix Shock Sx	High fever, diarrhea, sore throat, muscle pain, hypotension. 48 hr severe shock, liver, renal damage. Skin rash like scalded skin sx but deeper.	**Toxin – TSST-1** – direct and indirect effect **(super Ag)** via massive cyto release		Menstral –55%, highly absorbent tampons. **TSST-1 into blood.**
S. Epidermidis Hospital infections with catheters and prosthetic devices	Complicated UTI, Osteomyelitis, Endocarditis, Bacteremia (neonatal)	Normal flora of nose, skin, ear.	**BIOFILMS** – slime and PS/A in foreign body related infections	**Coag negative**, often xbio resistant. Non-hemolytic = white.
S. Saprophyticus	UTI (10-20%) mostly in women		Urease and stone formation	Not major hospital infection
Most S. Aureas are lysogenic w/phages. MRSA due to MecA on chromosome. Most staphy infections via autoinfection. PVL pos Staphy can cause rapid hemorrhagic necrotizing pneumonia, preceded by influenza-like Sx = poor prognosis. Pneumonia- fever, sudden onset, left shift, increase WBC, lobar consolidation.				

Streptococcal Sp. – Gram pos, spherical, pairs or chains, non-motile, **catalase neg**, hemolytic pattern on blood agar- alpha (green/brown), beta (clear), gamma (no rxn)

Name	Clinical	Pathogenesis	Virulence	Other
Strep Pneuomoniae – Gram pos, alpha hemolytic, lancet-shaped diplococci, catalase neg, 5-10% blood agar, bile soluble, suscept to optochin				
Major resp pathogen, **pneumonia, otitis media**, bacteremia, meningitis, septic arthritis, endocarditis. Most common pneumonia in US. Sinusitus, mastoiditus also.	Usually lobar pneumo, oldest part of lesion in center, chills, pleural pain, rusty sputum. Sample blood, CSF or sputum for capsular polysac.	Usually endogenous infection from pharynx to lung, mult in edematous fluid	**Capsular polysac** – antigenic, 90 serotypes, **anti-phago (major factor)-** interferes with depos of C3b – w/o capsule no longer pathogenic **Pneumolysin** – Membrane active toxin – damages pulm epi cells **Adhesins** – PspA and choline binding proteins, attach to pharyngeal cells	Less than 3 y/o and older than 70 y/o, previous bacteremia, serotype. Treat with amox, quinolone, 3rd gen cephlo, vanco. PCV7- Vaccine for <2y/o, capsule w/protein 23PS – Vaccine for bacteremia >65 y/o
Strep Pyogenes (Group A) – Gram pos, beta hemolytic, mucoid, catalase neg, PYR pos, bacitracin sensitive, protein A staphy test confirms				
Impetigo, Wound infections, pharyngitis, scarlet fever, toxic shock like Sx, cellulitis, nectrotizing fasciitis and myositis. **Rheumatic fever & Glomerulonephritis**	Pharyngitis – nausea, vomit and abdom pain Necrotizing fasciitis/myositis – exotoxin A and cysteine protease – flesh eating **Rheu fever** – anti-M Ig w/heart tissue **Renal** – Ag-Ig complex deposition in glomeruli	Scarlet Fever- Group A strain w/ toxin on phage.	Pili Lipoteichoic acid adhere to fibronectin **M protein – major factor – antiphago (90 serovars)** F protein – bind to fibronectin Hyaluronic acid capsule – antiphago **Group specific Lancefield CHO Ag** Streptolysin O – toxic to cells Enzyme debridgement C5a peptidase – No PMN's recog **Pyrogenic toxins – super Ag – scarlet fever and toxin shock like Sx**	Treat w/ Pen G. Group A toxin causes massive prolif of T-cells.
Strep Agalactiae (Group B) – gram pos cooci, beta hemolytic, catalase neg, bacitracin insensitive, CAMP pos, group B cell wall Ag with hyperimmune antisera confirms				
Neonatal meningitis**,** Pregnant - post partum bacteremia.	Early or delayed onset for neonates. Bacteremia and meningitis.	Immune surpressed adults- bacteremia, meningitis, cellulites.		Treat w/Pen G and aminoglycoside. **Prophylaxis during delivery w/GBS risk**

Name	Clinical	Pathogenesis	Virulence	Other
Group D Strep (two genera) – gram pos, alpha, beta or gamma hemolytic, catalase neg, bacitracin neg, hydolyze bile-esculin, **optochin resistant. Pg 188 differentiation of strep.**				
UTI, bacteremia, **endocarditis (worst),** wound and tissue infections			Enteroccus Fecalis – Pen R – only grow in NaCl. Strepto bovis – Pen S	Treat w/Pen G and aminoglycoside
Viridans streptococci (alpha hemolytic streptococci) – Gram pos cocci, catalase neg, alpha hemolytic, **optochin insensitive**, usually no dx				
Endocarditis 30-40% Dental Caries	Endocarditis usually after dental procedure with pre-existing damaged heart valves			Treat w/Pen G

<u>Neisseria Spp.</u> – Gram neg dipplococci, occur in pairs, non-motile, non-spore forming, aerobic and microaerophilic, oxidase pos (cyto C),. Pathogenic species do not grow at 22C, do not grow on agar w/o blood and need 5-10% CO2 fro optimal growth. Mucosal surfaces.

N. Meningitidis – w/ Strep pneumo most common cause of bacterial meningitis between 1 month and 59 yrs. Serotypes A,B,C,L,X,Y,W-135				
Bacterial Meningitis Waterhouse-Friderichsen Sx – bleeding into adrenal gg. **Very susceptible if complement deficiency.**	5-25%-Asx pharyng carriers Carriers -enhanced immunity Meningococcemia = meningococci in blood Shock, DIC, bilat adrenal loss. **Head ache, fever, stiff neck and petechiae.**	Cocci cannot survive in PMNs. Recovery without xbio dependant upon development of IgG anti-capsular antibodies	**1) Poly sacc capsule – 13 serogroups – present in blood and CSF – major factor - antiphagocytic** 2) Outer membrane proteins – Ig against protect host 3) LOS – endotoxin containing blebs 4) Protease cleaves sIgA 5) Sialyated LOS – blocks comp deposit – no C3b recog by phagos 6) Pili – attach to pharyngeal epi cells 7) Acquire iron in vivo	Incidence varies with serogroup and geo location. Spread human to human via pharyngeal droplets. Treat w/Pen G. Immunity develops with age. Vaccine available for serotypes except group B

Strep, Staph, Neiss all cocci, pyrogenic, invasive, pus lesions, extracellular, killed w/in phagos and have anti-phago virulence factors. Exception is N. gonorrheae.

Mycobacterial Infections **– Respiratory TB (M. tuberculosis, Intestinal TB (M. Bovis), Mycobacterium avium complex (MAC-opportunistic in respiratory tract), Leprosy (M. Leprae)**

M. tuberculosis – rods, non-motile, non-spore forming, acid-fast aerobes, cell envelope, slow growth, requires CMI for control, no CMI therefore death during primary infection, no toxins. **Acid fast.**				
Name	Clinical	Pathogenesis	Virulence	Other
Respiratory Infection	Tissue hypersensitivity at 6-14 wks, tissue necrosis and tubercle formation. Ghon complex (primary lesion) – tissue necrosis & calcification.	Inhale bacilli in droplet. Deposit in alveoli. Digestion by macro, mult in macro, macro lyse, macro coalesce and fuse to create granuloma with periph lymphocytes. Spread into lymphatics, blood and other organs. Contained by CMI (90% no dx). Reactivation triggered by immune comprimise or malnutrition. Caseous necrosis, tubercle formation and fibrosis in upper lung.	Bacilli are intracellular and inactive in chronic lesions. Treat with Isoniazid, rifampin, streptomycin, pyrazinamide, ethambutol or combos.	AIDS, homeless, crowding, poverty, infrastructure, refugees. HLA-Bw 15 freq clinical dx. With treatment – noninfectious in 2wks. Treat for 6 months must comply.
M. Leprae – Acid fast, **obligate intracellular**, spectrum of response dependant upon CMI activity. **Acid fast**.				
Skin Lesions	Usually lesions on extremeties, hands, feet, nose.	**TT- Tuberculoid** – High specific CMI response, CD4 T-cells in lesions/granulomas, demyelination of periph nn by macros **BB- Borderline** – intermed state, unstable **LL – Lepromatous** – Surpression of CMI – poor T-cell response, CD8 T-cells in lesions.	Nerve destruct in TT, disfiguration. Skin scrappings in LL and BL.	Human to human xfer, low infectivity, LL pts have high conc of bacilli in nasal discharge. 3-10 yr incubation period. Treat with dapsone. No vaccine.

Corynebacterium –

C. Diphtheriae – Diptheria
C. Ulcerans and C. PseudoTB – occasional disease in humans
C. Jeikeium – dx in severe immune surpressed pts, resistant to mult xbios
C. Urealyticum – UTI and alkaline encrusted cystitis
Several other C. spp. – normal flora, low virulence

C. diphtheriae – gram pos, club shaped, non-motile, nonspore, catalase pos, arranged in Chinese letters. Gravis, mitis and intermedium biotypes, not normal lab diagnostic, grow on tellurite. Model for toxin-mediated bacterial disease. **Cutaneous infection from non-toxic strain.**				
Name	Clinical	Pathogenesis	Virulence	Other
Upper resp tract infection **(toxic strain)**	Sore throat, low fever, pseudomem on tonsils, pharynx and nose. Myocarditis and polyneuritis complications.	Toxin frags A and B. B – receptor, A - xport to cytosol catalyzes xfer of ADP - ribose from NAD to EF-2 therefore no protein syn	Toxin – present in toxin corynephages – phage beta, produced under iron-limiting conditions. Toxin syn surpressed by iron-depend repressor.	Prevent via toxoid vaccine (DtaP). Treat with horse antitoxin and xbios. Neutralize toxin but still have colonies.

Listeria – pathogen for animals and humans, meningitis or septicemia in immune suppressed pts. Pregnant women infection can cause stillborn, abortion, or infant infection. **Food borne grows in cold or moderate temps.**

L. monocytogenes – short gram pos, motile rod, nonspore forming, facultative intracellular, catalase pos, beta hemolytic, grows on tellurite, CAMP pos, 13 serotypes – 1a,1b,4b pathogenic,				
Name	Clinical	Pathogenesis	Virulence	Other
Meningitis or Septicemia	Immune surpressed pts (70%) Pregnant women Influenza type sx, diarrhea, 1 wk after eating contam food. High fever, headache, neck stiff	Enter cells via surface protein **internalin**. Produces **LLO** to release rod from phagosome into cytoplasm. Mult in cyto. Move to other cells via **ActA** w/o entering xtracell space.	**LLO** – sulfhydyl-depend hemolysin – **essential factor**	Infections terminated by CMI response. Treat with TMP/SMX, penicillin, ampicillin, gentamicin. **Not w/ cephalosporin.**

Haemophilus – gram negative coccobacilli (curved ends on short rods), pleomorphic, non-motile, non-spore forming, fastidious – require X and/or V factors on chocolate agar.

H. influenzae – Six capsular types (a-f), **systemic dx mostly type b capsule** (polyribose-ribitol phosphate) PRP				
Name	Clinical	Pathogenesis	Virulence	Other
Type b (meningitis, epiglottitis, pneumonia w/empyema) **Nontypeable** (acute otitus media, sinusitis, community pneumonia, worsen COPD, acute RTI in kids, conjunctivitis, neonatal/maternal sepsis, bacteremia and invasive infections)	Bacteremia worse w/o normal spleen. Treat with 3rd gen cephalosporin first then try ampicillin.	Enter nasopharynx, invade resp epi cells and then cause various inflammations. Into CNS from blood not direct infection.	**Capsule is antiphagocytic, Ig against capsule is protective, causes complement phagocytosis.** Specimens in blood, CSF and synovial. Anti IgA protease.	No capsule forms are normal flora of URT – can cause otitis media. Aggult rxn detects free capsule Ags. Most cases in very young or old adults. Vaccine – Hib coupled to DtaP, PRP capsule conjugated to protein.
H. parainfluenzae – normal flora URT – can cause endocarditis				
H. aphrophilus – normal flora URT – can cause endocarditis or brain abcesses				
H. influenzae (biotype aegypticus) - causes conjunctivitis and Brazilian pupuic fever				
H. ducreyi – causes chancoid or soft chancre – ragged ulcer on genitals, enlarged region LNs, associated with poor hygiene				

Moraxella – gram negative coccobacilli, oxidase pos, some require enriched media to culture. M. catarrhalis normal flora in URT but can cause otitis media and pneumonia, penicllin resistant.

Bordetella – gram negative, short coccobiacilli, pleomorphic, oxidase pos, **encapsulated when virulent**. B. parapertussis may cause pertussis like dx.

B. Pertussis –requires enriched media BG agar or charcoal agar with horse blood				
Name	Clinical	Pathogenesis	Virulence	Other
Whooping cough (humans only)	**Very contagious**. Incubates 7-10 days. Catarrhal – cold sx, most contagious. Paroxysmal – freq violent coughing. Convalescent – slow persistent cough. **Nasal pharyngeal swab to sample.**	Colonize bronchial epi via adhesins, local damage via tracheal toxin, impairs host immune response via hemolysin, systemic effects via pertussis toxin. Toxins coordinately regulated.	**1) Pertussis toxin**- lymphocytosis promoting factor. Activates Gi via ADP Ribosylation. Raises cAMP therefore secretion in URT 2) **Xtracell adenylate cyclase** – like EF of anthrax toxin. 3) **Adhesive factors** – hemagglutinin & pertacin 4) **Tracheal cytotoxin** – destroys ciliated epi cells	**Kids less than 4 y/o**. Treat sx or with erythromycin.. Natural immunity with age, DtaP (purfied inactivated bacterial products)

Mycoplasma – smallest free-living organisms, membrane w/sterols, no cell wall thus pleomorphic and no muramic acid or peptidoglycan, **media require sterols**, binary fission, most normal flora, 3 human pathogens.

M. pneumoniae – extracellular				
Name	Clinical	Pathogenesis	Virulence	Other
Primary atypical pneumonia – walking pneumonia Tracheobronchitis Wheezing in Infants Pharyngitis Rhinitis	Extensive but patchy pulm infiltration, fever, malaise, myalgia, sore throat, cough. Insidious onset. 3wk incubation. Mild pneumonia, usually no hospitalization	Inhale resp secretions, attach to LRT, interfere with ciliary action. X-ray looks much worse than sx.	P1- attachment factor Cell membrane receptor – neuraminic acid w/glycoprotein	Isolate bug from sputum. Treat with tetracycline and erythromycin
Ureaplasma urealyticum – nongonococcal urethritis, poss cause infertility, genital.				
M. genitalium – nongonococcal urethritis, poss cause infertility, genital.				
M. hominis – poss role in pelvic inflamm dx, genital.				

Legionella sp. – new family of bacteria

L. pneumophilia – gram neg rod, non-spore forming, growth over wide-temp range, **fastidious (cysteine/iron),** BCYE medium, slow growth, oxidase and catalase pos, **facultative intracellular**, 85% of legionellosis				
Name	Clinical	Pathogenesis	Virulence	Other
Legionnaires' dx – acute pneumonia **Pontiac Fever** – acute self-limited fever, no pneumonia **Atyp pneumonia**	Fever, malaise, chills, cough, diarrhea, headache, chest pain hyponatremia. Lung lesions with PMNs and macros in alveolar spaces. Long incubation.	Inhalation of aerosol, evades host defense and enters monocyte in LRT. CMI important in defense.	Syn beta-lactamase, hemolysin, cytotoxin. Treat with erythromycin plus support. **Bugs in bronchia and antigens in urine. Live in protozoan in contaminated water.**	Bug from contaminated water sources. AIDS, chronic CV, age, smoking at higher risk.

Chlamydia sp. – broad spectrum of diseases (acute, chronic, persistent, inapparent), obligate intracellular, binary fission, cell envelope similar to gram neg but no peptidoglycan (impact of xbio selection?), carry plasmids, dimorphic life cycle (EB and RB), mult w/in inclusion vacuole (no fusion with lysosome). Culture growth is slow, hard and expensive. Diag via staining and detection of intracytoplasmic inclusion bodies.

C. trachomatis – Serovars A, B, Ba and C			
Name	Clinical	Pathogenesis	Other
Trachoma – follicular conjunctivitis	Chronic infection cause pannus, scarring and deform of eyelid and **scratching of cornea then blindness**.	Bugs into eye by contaminated hand. Grows in epi cells. Immune rxn causes follicular conjunctivitis, heal or chronic.	Leading cause of preventable blindness. High in Africa/Asia.
C. trachomatis – Serovars D-K – most common cause of STDs in US			
Adult Inclusion Conjunctivitis	Conjuctivitis with edema, erythema and pus discharge. No scarring or pannus therefore **no blindness**		Associated with STDs
STD: Men – non-gonococal urethritis, acute epididymitis	Urethral irritation and leukocytosis		M-F xfer is 70%, 20% with GC
STD: Women- Acute urethal sx Pus cervicitis, salpingitis, PID	Most women Asx or subtle. Cause sterility, ectopic, miscarriages, low weight babies	Can have inapparent genital infection with inclusion conjunctivitis. 50% with tube scarring w/o PID	F-M xfer ~ 33-50%. ~25-65% with GC
Neonatal Infections – Occular or interstitial pneumonia	Pick up bug in eye during birth. Also nasopharynx, rectum and vagina.	Pneumonia – gradual onset no fever.	

Name	Clinical	Pathogenesis	Other
C. trachomatis – Serovars L1, L2, L2a and L3			
Lymphogranuloma venereum - LGV	**Primary lesion** – small, painless vesicle on genitalia. Heals spontan. **Weeks later** – regionally enlarged LNs (buboes). Fever, chills, headache, arthalgia and myalgia. **Late**- abscesses and fistulas	LGV strains show tropism for lymphoid cells.	Many infections inapparent.
C. psittaci -			
Psittacosis	Atypical pneumonia with high fever	Inhale dust from infected bird droppings.	
C. pneumoniae			
Walking pneumonia	Clinical like M. pneumoniae	Human to human via resp droplets	Assos with coronary heart dx.

Treponema sp. – spiral shaped, no gram stain use darkfield or fluorescent staining of antibodies.

T. pallidum – very low infectious dose, spread via sex or congenital,requires enriched media BG agar or charcoal agar with horse blood				
Name	Clinical	Pathogenesis	Virulence	Other
Primary Symphilis – lesion- chancre	Chancre heals spontaneously, but systemic infection continues asx.		Systemic spread has occurred with appearance of chancre, 2-10 wks after infection.	Syphilis with HIV is much worse. **Treat with Pen G for all syphilis forms.**
Secondary Symphilis – lesions of skin, mucous mems	Lesions – 2-10 wks after chancre heals. Heals spont but infection continues asx			Uncommonly causes meningitis, iritis, hepatitis, etc.
Latent Symphilis – Asx infection	Early latent < 1 year Late latent > 1 year		Infectivity of body fluids declines with time during latent stage	
Tertiary Symphilis – Asx infection	Syphilitic aortitis, CNS effects, late benign bummas	Years later, 33% of untreated pts		

Borelia sp. – spiral shaped, no gram stain use Giemsa or Wright stain. Can be cultured but fastidious and microaerophilic.

B. recurrentis –				
Name	Clinical	Pathogenesis	Virulence	Other
Relapsing Fever – lice and tick xmit.	Recurrent fever with asx intervals. Lice – epidemic form. Tick– endemic form.	Person to person by lice or animal to person by ticks.	Ticks can be reservoir and vector.	Ig cycle vs antigenic variant (gene recombination)

B. burgodorferi –				
Lyme disease	**Stage 1-** local infection – erythema migrans **Stage 2** – dissem infection – annular skin lesions, malaise/fatigue **Stage 3** – persist infection – arthritis, neuropathies, meningoencephalitis	Culture only pos in pts with EM lesions	**Ixodes scapularis** vector primarily nymph stage	Deer important in life cycle.

Leptospira sp. – spiral shaped, no gram stain, very thin use darkfield microscopy and silver stains. Causes leptospirosis - zoonotic dx worldwide. **Poor Puddles and Red Eyes.**

Name	Clinical	Pathogenesis	Virulence	Other
Leptospirosis – Flu –like - fever, conjunctival suffusion, renal failure, meningitis, encephalitis.	**Weil's dx**- renal failure **Icteric** – serious **Anicteric** – less serious	Contact with infected urine from animals in soil or water.		Hangs out in renal tubules of rodents. Human contact w/urine contaminated water or mud.

Neisseria Spp. – Gram neg cocci, occur in pairs, non-motile, non-spore forming, aerobic and microaerophilic, oxidase pos (cyto C),. Pathogenic species do not grow at 22C, do not grow on agar w/o blood and need 5-10% CO2 for optimal growth. Naturally competent for DNA transformation and conjugation w/large conj plasmid. Some transposons w/tetracycline resist on plasmid. Some have 2nd plasmid with beta-lactamase that can be xferred if conj plasmid is present.

N. gonorrhoeae – Non-sexual xmission is rare

Name	Clinical	Pathogenesis	Virulence	Other
Asx	Major reservoir of infection. 10% M, 50% F.	Adhere to lower genital tract via pili assisted in entry via Opa. Bug sensitive to low pH. Iron in blood and reflux of menses helps bug. In fallopian tubes, bug adheres to nonciliated epi cells. Damage by LOS and PG frags. DGI assos w/strains w/porins that slow complement-mediated killing.	**Colonization pili** – w/ pilin – adhere to epi cells & young sperm **Opacity proteins (Opa)** – 12 types per strain. **LOS** – within blebs on outer mem – phase and Ag variation and sialyltransferase – resist complement mediated lysis. **Antigenic and phase variable surf proteins** – evade immune sys Iron binding proteins – compete w/host **IgA1 protease** – cleaves IgA1 **PI protein** – major porin – toxic effects and slow complement activation **Catalase** – protect bugs from oxidative burst by polys	Repeated infection is common – antigenic and phase variation.
Urethritis	Freq, urgent painful urination. Yellow pus with bugs and polys.			High incidence in adolescents.
Cervicitis or vulvovaginitis	Inflamm of endocervical canal with pus, bartholin gg and poss abscesses.			Diag in men via urethral discharge. Women PCR b/c of flora.
Rectalitis	Mostly asx, tenesmus, pain on defecation.			**Treat for Clamydia at the same time.**
Pharyngitis	Mostly asx, sore throat			No vaccine.
Ophthalmia neonatorum	Neonates during birth			
Localized dissem in reproduct tract	Men – epididymitis, prostitis Women – endometritis, salpingitis, PID, CFH Sx into peritoneum from fallopian.			In women can cause pelvic pain, infertility and ectopic
Dissem Gonococcal Infection (DGI)	1-3% of local infections mostly women. Dermatitis – bloody popular lesions and arthritis in large joints.		**PID and DGI often before or during menses.** Complement deficiency is a high risk factor	Uncommonly in heart or meninges

N. Gonorrhoeae – uses glucose but not maltose
N. Meningitidis – uses glucose and maltose
Both lactose and sucrose negative.

Name	Clinical	Pathogenesis	Virulence	Other
Bacterial Vaginosis – massive overgrowth of normal flora.	100-1000 times than normal. Abnormal vaginal discharge, thin, milky smelly. **Clue cells** – epi cells with bugs attached.	Inhibit normal lactobacilli therefore raise pH and loss of H2O2 production	PH change increase normal flora G. vaginalis and Mobiluncus sp **(more succinate – less WBCs)**. Also increase T. vaginalis due to more favorable environ.	Caused by sex, menses, douching.
T. Vaginalis – pear shaped flagellated protozoan, STD pathogen, non-sex xmission is very rare, many asx in men and women, most women also have BV, binary fission. Lives in vagina, urethra or prostate. Aerotolerant anaerobe. Unique hydrogenosome for energy.				
Post Partum endometritis Premature labor, low birth weight, cervical erosions, cervical dysplasia/cancer	Degen, desquam vag epi cells. 20-50% asx. Vulvovaginitis, pruritis, itching, inflamm. Pus, thin, colored smelly discharge. Painful sex. **Strawberry cervix.** Most have BV-85%	Bug is chemotactic for polys. Recurrence is common. More common but not more severe if immunocompromised. Most men Asx – pain on urination, tender prostate.	Cytoadhere and cytotoxic Adhesins Surf cysteine proteinase Surf glycoprotein phenotypic variation if contains dsRNA virus. Considered non-invasive.	Most prevalent non-viral STD in world. **Pyruvate-ferredoxin oxidoreductase** energy ENZ target for **Metronidazole. If diag always look for other STD bugs.**
Candida – yeast vaginitis – proliferation of normal vaginal yeast. White, cheese or curd-like discharge with WBCs, many triggers.				

Rickettsia sp. – gram neg coccobacilli, pleomorphic, obligate intracellular, Giesma stain, not free-living (need host ATP and leak NAD). Spread to cells via actin polymerization (like Listeria and Shigella). Isolation of bug is difficult and dangerous, look for Igs in serum via agglutination, immunofluoresce and complement fixation tests.

R. prowazekii – Epidemic Typhus – Louse-borne (Pediculus corporis), human primary reservoir.				
Name	Clinical	Pathogenesis	Virulence	Other
Epidemic Typhus	Skin rash, fever, severe headache, malaise, laidup. Big liver and spleen. Rash starts in axilla and **spreads outward.** No face, palms or soles.	**Vasculitis** – proliferation of bugs in endo lining of small aa., vv. and caps.	**Brill-Zinsser** – recur from old infection.	Person to person xmit by lice. Lice feed and purge at same time.

R. Typhi – Endemic Typhus – common soluble Ag with R. prowozekii, humans accident host. Rat-flea-rat normal.				
Name	Clinical	Pathogenesis	Virulence	Other
Endemic Typhus (murine typhus)	Similar to Epidemic Typhus but milder sx. Rash starts on trunk.			
R. Rickettsii – **Rocky Mountain Spotted Fever** – most common rickettsii infection in US. Vectors – Dermacentor andersoni (wood tick) and D. variabilis (dog tick).				
RMSF – often children	Acute, severe febrile dx with myalgia, malaise, late rash starting on extremities and **moves proximally**.	Involves palms and soles.		
R. Akari – Rickettsial Pox				
Rickettsial Pox	Mild zoonotic and febrile dx. Rash like chicken pox (varicella).	Mouse mites to human xmission. Painless papule than ulcers and forms eschar at bite site.		

Ehrlichia sp. –

E. chaffeensis – xmitted by ticks and D. Variabilis (dog tick) – infects human monocytes				
Name	Clinical	Pathogenesis	Virulence	Other
Human monocytic ehrichiosis (HME)	Looks like RMSF but little rash and only 1/3 of cases.			
Anaplasma phagocytophiilum – xmitted by ticks that can co-xmit Lyme Dx				
Human granulocytic ehrichiosis (HGE)	Looks like RMSF but little rash and only 1/3 of cases.			

Others –

Coxiella burnetii – very resistant to drying, and physical agents, no agglutination to Proteus X Ag, xmit to humans via aerosols.				
Name	Clinical	Pathogenesis	Virulence	Other
Q-Fever	Often Asx, infreq rash. Resemble influenza, nonbact pneumonia, hepatitis, encephalopathy.	Inhale airborne bugs. Assoc with goats, sheep, dairy cattle or cats.	Can cause endocarditis if previously damaged valves.	
Orientia tsutsugamushi – xmit to humans by bite from larval chiggers/mites (Leptotrombidium). **(Islands and Eschars)**				
Scrub Typhus –	Febrile, resemble epidemic typhus but eschar indicates bite site. Rash on trunk spreads distally. Regionally enlarged LNs	Eschar not as big as anthrax, mild pain, no bugs aspirated.	Vegetation harbors vector. The eggs of mites are infected (transovarial)	Only Far East – rats and mites.

Bartonella – grow in cell free media

B. quintana – Classical Trench Fever – Body louse vector Urban Trench Fever – Body louse vector, homeless people Bacillary angiomatosis – immunocomprimised pts
B. bacilliformis – Carrion's Disease – Sand fly vector
B. henselae – Cat scratch fever – zoonotic infection with fever, enlarged LNs, some visceral/osteolytic lesions. Probably flea vector., Bacillary angiomatosis - immunocompromised pts.

Yersinia pestis – gram negative coccobacilli w/bi-polar staining, facultative intracellular, not fastidious, virulence traits at 37C. Zoonotic infection, vector borne by rat fleas. Humans are incidental hosts. **Blockage in flea gut cause regurgitation therefore infected bite. Bugs grow w/in phagolysosome of macrophages.**

Name	Clinical	Pathogenesis	Virulence	Other
Sylvatic Plague	Most common in US. Bugs xfer by fleas from chipmunks, prairie dogs.		**Capsular Ag** – anitphago activity on chromosome **V Ag** – low Ca induces this gene on plasmid **YOP** – Yersinia outer mem protein – on plasmid blocks phago by macros	Prevent rat xfer via public health rat control. ID via **fluorescent Ig test** or **bi-polar staining rods** (safety pin look) with Wayson's stain. Immunity w/recovery via Ig against V Ag.
Bubonic Plague - Lymphadenitis	1-6 day incubation. High fever, tachycardia, malaise, arm/leg ache.	Painful bubo (tender enlarged LN). Most often axillary or inguinal.		50-70% if untreated progress to septicemia and/or meningitis. Die from gram neg septic shock.
Pneumonic Plague	2-3 day incubation. Fever, malaise and tight chest. Later productive cough, dyspnea and cyanosis.	5% of bubonic plague develop secondary Pneumonic plague. Poss human-human spread		100% fatal w/o therapy

Brucella sp. – Gram neg rods, fastidious, **slow growing (6wks),** facultative intracellular parasites of the reticular endothelium system (RES), zoonotic dx, humans accidental hosts, like to localize in pregnant uterus and mammary gg. Never human to human contact. Use 10% CO2 to culture.

Name	Clinical	Pathogenesis	Virulence	Other
B. melitensis	Incubate 2wks to several months. Insidious fever, night sweats, headaches. Chronic.	Bugs enters nasopharynx, skin or cut via contact w/sick animals. Placentas, milk or semen.	Bugs multiply in macros and hang out in phagocytic cells of RES. CMI is protective.	**Infected raw goat's milk.** Occupational hazard of people who work w/animals. Can only culture during active dx.

Francisella tularensis – Gram negative coccobacilli, facultative intracellular, grows slow (requires cysteine media), humans w/ direct contact to infected rabbits, muskrats, tick and deerfly bites.

Name	Clinical	Pathogenesis	Virulence	Other
Skin Pneumonic Typhoidal Oculoglandular	Skin infection - fever, headache, malaise, **bubo.** Typhoidal - ingestion. Pneumonic – aerosols 30% fatal. Eye - contamination	Xmission via skin from insect bite, contaminated water/food or inhale from lab accident	Rapid ID via fluorescent Ig test. CMI protects.	Low infect rate via skin or inhale. Wear gloves, protective clothing.

I) Herpesvirus

Diseases

1) Herpes simplex (fever blister)
2) Herpes zoster (chicken pox and zoster) – **VZV vaccine incorporated with MMR for 2 y/o, effective post exposure**
3) Mono
4) Burkitt's Lymphoma
5) Nasopharyngeal angiocarcinoma
6) Childhood exantem (eruption)
7) Kaposi sarcoma
8) Pleural Effusion lymphoma

Types

1) HSV-1 – neurons in trigem and cervical gang
2) HSV-2 – neurons in sacral gang
3) CMV – monocytes and endo cells
4) VZV – cells in sensory gang, trigem and DRG
5) EBV – B-cells
6) HHV-6 (human herpes virus) – monocytes, CNS, salivary gg.
7) HHV-7
8) HHV-8/KSHV (kaposi sarcoma herpes virus) – vascular endo cells, prostate, saliva

Structure and Classification

1) dsDNA in core with icosahedral capsid
2) outer envelope from host cell nuclear membrane
3) Alpha group – HSV-1, HSV-2, VZV – variable range, short cycle, latency in sensory ganglia
4) Beta group – CMV, HHV-6, HHV-7 – restricted range, long cycle, cytomegalia
5) Gamma group – EBV, KSHV, HHV-8/KSHV – easy infect, then latency in lymphocytes, can transform cells into malignancy.

Life Cycle Details

1) Take over cellular machines for macromolecular synthesis
2) Encode enzs for DNA replication
3) Some decrease MHC I expression
4) Syn proteins to prevent death or apoptosis
5) All establish latency
6) HSV binds to heparan sulfate
7) EBV binds to CD21
8) Almost all DNA viruses have a temporal organization (parts just in time for assembly)
9) Early genes- before the onset of DNA replication
10) Immediate early genes (alpha) – before protein syn, transcriptional activators
11) Delayed early genes (bravo) – require protein syn to express, proteins for DNA replication. Must have alpha genes to express
12) Late genes (gamma) – require protein syn to express, after DNA replication, mostly structural proteins
13) VP-16 transcription factor to turn on alpha genes

14) Alpha turns on bravo, bravo turns off alpha and turns on gamma
15) Unique DNA polymerase, DNA binding proteins and thymidine kinase from alpha and bravo genes only for viral replication. Therefore drug target.
16) DNA syn starts at origins of replication and proceeds as a covalently closed circle
17) Final virus assembly in nucleus, but slow or none if DNA syn is inhibited
18) Envelope from nuclear membrane (not cytoplasmic!) and exit through Golgi complex

Latency

1) Sites vary from neurons to lymphoid cells
2) Molecular switch in and out of latency unkn
3) EBV- prolif of B-cells, can become neoplastic (Burkitt's)
4) EBV- only 4-6 genes expressed to maint latency, Zebr/Zta gene product can switch virus back on
5) HSV in neurons, only expresses LAT (latency associated transcript), unkn function, not req for latency
6) EBV in B-cells, expresses LMP-1 and 2, EBNA 1,2,3A,3B,3C
7) Reactivation via transcriptional switch from various stresses

Human dx

1) Except for HHV-8/KSHV – very high percent of pop is infected with Herpes viruses
2) HSV-1 – labial lesions, skin lesions, encephalitis, 95% of orofacial herpes, 10-30% of primary genital herpes (but seldom recurs), 80-90% adults seropositive **(low level mashing)**
3) HSV-2 – recurrent genital lesions, neonates, pregnancy, immune surpress pts, may cause primary oral herpes (but seldom recurs), 20-40% adults seropositive **(high level mashing)**
4) VZV – chicken pox and shingles **(airborne droplets, low level mashing)**
5) CMV – birth defects, deafness, mono-like, pneumo in immune surpress pts **(perinatal, transplacental in 1st 6 months, high level mashing, blood donate, organ donate)**
6) EBV- mono, burkitt's, NPC, various B-cell prolifomas **(low level mashing)**
7) HHV-6&7 – roseola inflamm – 3 day fever infants and kids the eruption of rose colored spots **(low level mashing)**
8) KSHV – kaposi sarcoma **(high level mashing, blood and organ donations)**
9) Herpes B – Monkey HSV – human encephalopathy **(don't kiss a monkey)**

Acyclovir and Ganciclovir - (Herpes Thymidine Kinase)

1) Structurally diff from cellular TK
2) Homologue of deoxyguanosine
3) Only virus TK can add first phosphate to drug and start activation process
4) Further phospho by cellular GMP kinase to active compound – ACG-ppp
5) ACG-ppp inhibits DNA polymerase – therefore chain termination and cell death
6) Treat recurrent HSV and VZV infections
7) Acyclovir does not work against CMV w/o TK gene, therefore use ganciclovir
8) Ganciclovir – cause low polys and platelets, therefore only life threaten with immune surpress pts, poss treat for CMV
9) Valaciclovir – oral form of acyclovir, absorbed better therefore higher blood drug levels, use for symptomatic recur genital lesions
10) Famciclovir – oral, metabolized to penciclovir with a longer intracellular half life, use for symptomatic recur genital lesions.
11) Mutated virus to bypass acyclovir effects is less virulent

12) Acyclovir can cause renal dysfunction via crystallization if dehydrated

PAA and Foscarnet (PFA) - (Herpes DNA polymerase)

1) Structurally diff from cellular DNA polymerase
2) Virus version higher affinity for PFA
3) Bind pyrophosphate site of polymerase
4) Liver and kidney toxicity
5) Foscarnet - HSV and CMV infections

More diseases

1) HSV-1
    a. Infections xmitted via asx shedding, but infection risk is greater w/lesions.
    b. Virus does not penetrate intact skin
    c. Gingivostomatitis- most common clinical sx, mostly kids less than 5 y/o. Severe mouth pain with fever, sore throat, cervical adenopathy, and pharyngeal edema
    d. Recurrent herpes labialis – cold sores, fever blisters. Dormant in trigem ganglion.
    e. Vesicles crust over in 48 hrs, heal 5-7 days, rarely systemic sxs during recurrence
    f. Whitlow – HSV infect of finger. Usually HSV-1
    g. Keratoconjunctivitis – usually HSV-1, infect cornea and conjunctivae – most common cause of corneal blindness in US
    h. Extension to areas of eczematous skin or abraded skin from wrestlers
    i. Encephalitis in kids or young adults (primary) or adults over 50 y/o (recur). Temporal lobe.
2) HSV-2
    a. Most common cause of genital ulcers in US. Primary with fever, malaise, inguinal LNs
    b. Autonomic nervous system, Acute aseptic meningitis
    c. Recurrent genital herpes, less severe and shorter than primary
    d. Perirectal in homosexual men
    e. 40-50% risk to neonates if lesions present at delivery
    f. Detect via Tzanck prep, Viral culture, Immunoperoxidase-linked Ig's, PCR, Serology

3) Herpes-B
    a. Like herpes simplex in monkeys, xmit via monkey bite.
    b. High incidence of neuro complications
    c. Rare asx infections

4) VZV – Varicella-Zoster
    a. Primary-Chickenpox, Recur – Shingles
    b. Very contagious via airborne spread
    c. Lesions of various stages occur simultaneously
    d. Bacteria may infect lesions – increase scarring risk
    e. Tzanck prep or skin biopsy – does not disting btwn HSV
    f. Possible pneumonia, encephalitis, cerebellar ataxia in kids, Reye's sx (enceph w/ hepatitis, aspirin use), bullous or hemorrhagic with AIDS
    g. Worst for neonate, when mom has primary infection just before delivery

h. Give post exposure prophylaxis to sero neg if pregnant, pre-mature baby, immune surpress, lymphoma/leukemia
i. Vacinne 70-90% effective, reduce severity in the rest

5) VZV – Herpes-Zoster
   a. VZV latent in sensory gang after chickenpox
   b. Dermatomal zoster often in immune surpressed. Increases with age, 10-20% of adults.
   c. Disseminated form often with pain and neuralgia (cranial nn)
   d. Difficult to grow in culture

6) EBV
   a. 80-100% of pop, minority get IM
   b. Spread by asx people
   c. Fever, pharyngitis, enlarged LNs, splenomegaly, big liver
   d. Skin rash from ampicillin/amoxicillin, some hematologic and neurologic complications
   e. Burkitts, Nasopharyngeal carcinoma, Oral hairy leukoplakia, lymphomas, post-xplant lymph disorder
   f. Atypical lymphocytes (Downy cells)

7) CMV
   a. 50% US seropositive
   b. Blood is not screened for CMV
   c. Mostly Asx
   d. Immunocompromised host – Retinitis, pneumonitis, colitis, esophagitis, neuropathies
   e. Congenital – common if primary infect in mom 3rd trimester – intelligence and hearing loss in survivors
   f. Virus shed in milk, saliva, urine, cervix
   g. Look for intranuclear inclusions on histology (owl eye), CMV antigen in polys for blood culture test for BM xplant pts

8) HHV-6
   a. IM like sx in adults – atypical lymphos, no fever, big LNs
   b. Exanthem subitum in infants (rose colored spots), Roseola
   c. Systemic infection in AIDS – pneumonia, BM surpression, encephalitis
   d. 90% infected by 3 y/o

9) HHV-7
   a. Most US infected – can cause roseola

10) HHV-8
   a. Less than 10% US seropositive
   b. KS lesion with AIDS

II) Adenoviruses

1) Non-enveloped with icosahedral capsid

2) Linear dsDNA
3) Common infections, limited disease
4) Serotypes 3,4,7 ARD in boot camps
5) Persist in tonsils, 5% of all acute resp tract illnesses
6) Vector used for gene xfer
7) Easy culture growth
8) Highly stable to drying, GI acid, mild chlorine
9) Replicated in epithelial cells
10) Fiber projections from 12 vertices interact with CAR – coxsackievirus and adenovirus receptor
11) Early gene expression blocks p53 - cellular apoptosis
12) DNA replication in nucleas 6-9 hrs post infection
13) Large intra-nuclear inclusion bodies
14) No assos with human malignancy
15) Vaccine for serotypes 4 and 7
16) Causes pharyngitis, fever, ARD, conjunctivitis, diarrhea, bladder/urethra/cervix infections
17) Systemic infections with AIDS, pneumonia, hepatitis

III) Parvoviuses

1) Erythrovirus (B19) – only parvoviruse known to cause dx in humans
2) Aplastic crises w/sickle cell and hydrops fetalis(anemia and CHF in fetus) in seroneg pregnant women
3) Xmit via resp droplets and oral secretions
4) Non-enveloped with icosahedral capsid
5) Linear ssDNA
6) NS – nonstructural Rep protein for cutting replicative DNA and unwinding viral DNA
7) CAP for viral structural proteins
8) Package both + and – sense DNA
9) Very dependant upon host functions to replicate
10) Defective AAVs require host cell machines and helper virus to replicate
11) Erythima infectiosum – Lacy, mascular rash (slapped cheek) on face, spread to trunk and extremities, 80% arthritis especially in women
12) Mostly Asx infections
13) Viremia that can cross placenta
14) No Vaccine
15) Transient depletion of eryth precursors and decreased RBC syn
16) AAV under study as DNA vector for chromosome 19

IV) HPV – Human papillomaviruses

1) Replication linked to differentiation of squamous epithelium.
2) No lab culture because terminally differ keratinocytes cannot be maintained
3) Genome in low copy numbers in episomal state in undiff basal cells
4) Virus rep coordinated with growth and movement of cells to surface
5) E6 and E7 target tumor suppressor genes p53 and Rb, activate cyclins A and E, transforming genes
6) Subtypes 16 and 18 assos with cervical cancer
7) HPV-16 L1 (major structural protein) vaccine prevents HPV-16 infection in women

8) Cause genital and non-genital warts (papillomas)
9) No envelope, dsDNA covalently closed circular. E1-E7 early gene products, L1 and L2 capsid proteins, E6-L1 non-coding control region.
10) Induce squamous and fibroepi tumors
11) Most common types infect hands and feet causing warts
12) Assos with cervical cancer (16&18), tumors of the ano-genital area, and non-melanoma skin cancers
13) E6 and E7 onco-proteins are maint and expressed in progressed HPV tumors
14) No vaccine, L1/L2 proteins spont assemble into virus-like particles – genotype specific
15) E6 degrades p53 – stops negative regulation of cycle-dep kinases – cells do not stop at S phase
16) E7 inactivates pRB – retinoblastoma tumor surpressor – no interaction with E2F transcription factors – lose control of cell syn and growth

V) Polyoma Viruses

1) Not known to cause human cancer
2) SV40 – Simian vacuolating virus 40 – induces tumor in rodents
    a. Must continually express tumor antigens to cause transformation
    b. Large and small T-antigens (tumor)
    c. Inactivates p53 and pRB
    d. Early contaminate of polio and adeno vaccines
    e. No link to human malignancy
3) BKV- hemorrhagic cystitis, ureteral stenosis and UTI, reported in several human tumors
4) JCV – progressive multifocal leukocephalopathy – demyelinating dx of CNS w/AIDS, kidney, lymphos
    a. 70-100% seropos in humans, usually Asx
    b. With BKV, produce T-antigens related to SV40T

VI) Other DNA Onco-Viruses

1) EBV
    a. Infects B-cells and epi cells
    b. Can progress to B-cell lymphomas
    c. NPC – reactivated EBV expresses Latent Membrane Protein -1 (LMP-1)
    d. LMP-1 interacts with TNF to cause cellular activation
    e. Burkitt's Lymphoma – not always EBV
        i. C-myc translocation from 8 to Ig locus on 14 – increased expression
    f. Lymphoproliferative Disorders w/AIDS
    g. Hairy leucoplakia with AIDS
    h. Parotid
    i. T-cell Lymphomas
    j. Hodgkin Lymphoma – R-S cells with EBV

2) Kaposi Sarcoma/HHV-8
    a. Found in all 4 forms of KS – classic, edemic, epidemic, iatrogenic
    b. Infects vascular endo cells and B-cells
    c. HHV-8 genome has homologues to IL-6, IL-8 and BCL-2

VII) Viral Gastroenteritis

General

1) Viruses responsible for ¾ of all infective diarrheas
2) Tough to grow in culture
3) 2nd most common viral illness after URI
4) Rotavirus (dsRNA) cause deadly diarrhea in infants
5) Major killer of undernourished infants
6) Norwalk & other Caliciviruses (pos sense, ssRNA) cause epidemic gastroenteritis in kids and adults
7) No fecal polys with Viral Gastroenteritis – therefore distinguish from bacterial infection

Viral Gastroenteritis

1) Rotaviruses, Adenoviruses 40/41, Caliciviruses, Astroviruses, Coronaviruses (order of importance)
2) 2nd most common disease in US (16%) after common cold, **peak in winter in US**
3) Short incubation and short duration
4) Diarrhea, vomit, nausea, GI cramping, muscle aches and fever
5) Study via ELISA of viral antigen or antibody screening
6) Mult serotypes, no cross protection, immunity short lived
7) **Fecal/oral spread**, unwashed hands.
8) Difficult to ID causing virus

Rotavirus

1) Icosahedral, dsRNA, 11 segments, no envelope, double shell capsid
2) 4 serotypes, reassortment with related species
3) Fast replication (12hrs) in cytoplasm
4) Infectious after proteolytic cleavage of outer capsid protein VP4 by GI acids
5) Infects villi of SI, damages xport system of sodium and glucose – osmotic diarrhea
6) Treat with oral rehydration therapy
7) Serotypes 1-4 infect humans
8) VP4 and VP7 (outer surface proteins) are type specific antigens
9) Local immunity from IgA and interferon, does not protect against other serotypes
10) Diag via virus in stool or Ig titer

Caliciviruses

1) No envelope, linear pos sense ssRNA
2) Most important are Norovirus and Sapovirus usually infect adults
3) **Norwalk and Noroviruses**
    a. Cannot culture in cells or animals
    b. Very stable to heat and chlorine
    c. **Vomit more than diarrhea**, no blood, winter vomiting dx
    d. Broaden and blunt villi of prox SI w/intact mucosa, mono infiltrate and cyto vacuolization
    e. Fecal-oral spread, seafood and shellfish, common foodborne, cruise ships, oysters
    f. Agent of gastroenteritis in military
    g. Diag: vomiting, 12-60hr illness, incubate 24-48 hrs, no polys in stool
    h. Virus capsid in the major antigen, ELISA, PCR, immune-electron microscopy
    i. Treat with fluids and electrolytes

j. Capsid antigen used for edible vaccines

4) **Sapovirus**
   a. Epidemic outbreaks, kids have Ig's by 3 y/o
   b. 5 distinct antigenic types, usually not severe in infants
   c. May cause **more frequent diarrhea than vomiting**

Adenoviruses – Types 40 and 41

1) Naked dsDNA virus
2) Endemic in young kids and neonates
3) Lasts for more than 7 days (distinct)
4) Diag via EM or antigens in feces by ELISA

Astroviruses

1) No envelope, pos sense ssRNA
2) Humans and animals, usually cause GI sxs
3) Common in kids in Thailand and Guatemala
4) 8 serotypes, **can grow in tissue culture**
5) Fecal-oral xmission
6) Endemic gastroenteritis, usually in young kids and neonates
7) Usually not in adults, winter/rainy assosciation
8) Most people have Ig's by 6-9 y/o
9) Stool with many viruses unlike Noroviruses

Coronavirus – Human Torovirus

1) RNA with crown-like appearance
2) Unconfirmed assos with GI sxs in humans, certain in animals.
3) Spike glycoprotein – poss vaccine development
4) SARS – corona virus with pneumonia and travel history

VIII) Hepatitis

1) Immuno assays are available for each hepatitis virus
2) B,C and D cause chronic hepatitis and also cause liver cancer
3) B and D are tightly assosciated
4) Vaccines exist for A and B. B vaccine protects against B and D

Hepatitis A – picornaviridae family

1) No envelope, pos sense ssRNA, no segments
2) Replicates in cytoplasm
3) Fecal-oral spread, poor sanitation
4) 20% of hepatitis in US
5) Often Asx
6) Transient viremia – HAV specific IgM antibodies
7) No chronic hepatitis or liver cancer, self-limited infection
8) Killed vaccine, prior infection protects

9) Immunoprophylaxis with protect Ig before infect or before symptoms develop

Hepatitis B – hepadna family

1) HBcAg(core), HBsAg(surface), dsDNA (covalently closed circular), DNA polymerase
2) No in vitro cultures
3) CCC DNA directs transcription of large RNA using host RNA polymerase II in nucleas
4) Viral reverse transcriptase syn viral DNA in cytoplasm. Similar to retroviruses HIV and HTLV
5) Replication in hepatocytes, ags in both nucleus and cytoplasm.
6) Replication does not damage the cells, immune response mediated.
7) Chronic shedding of HBsAg
8) Infants at higher risk for chronic infection, and risk for liver cancer. Freq chromosomal integration
9) Blood is highly contagious, STD, shared needles
10) Primary cause of HCC
11) Early infection detect DNA polymerase, virons, core and surface Ags
12) Development of anti-Hbe is good prog assos with clearance of infected hepatos and end of viral replication
13) Surface Ag in blood for months, ends with anti-HBs and marks end of persistent viral shedding
14) Chronic carriers never develop anti-HBs and shed for life, poss chronic immune complex dx
15) Pre-existing anti surface Ig prevents reinfection
16) Subunit vaccine of HBsAg is prepared from pts blood, but cloned subunit vaccine is safer.

Hepatitis D

1) Circular ssRNA – rigid rod shape similar to plant virons
2) Replication – RNA cleaves itself at one site on genomic RNA and one on the anti-genomic RNA
3) Virons can only be formed with help from HBV
4) HDV core and HDV envelope with HBsAg
5) HDV neurtralized by anti-HBsAg
6) HDV can only exist in the presence of chronic HBV infections, therefore blood products or IVDUs
7) Acute fulminant hepatitis in HBV+ people with high HDV infection

Hepatitis C - Pestivirus

1) Blood borne hepatitis clinically similar to HBV
2) Major cause of non Hep A, non Hep B hepatitis
3) 80% of infections become chronic, contrast with HBV
4) Acquire from mult transfusion or IVDU
5) 50% response from interferon alpha plus ribavirin
6) Pos sense RNA genome, highly mutant, many genotypes
7) Proteolytic cleavage by host and viral proteases
8) Detected via cloned viral sequence and viral Ags
9) EIA for Nucleocapsid C22 and non-structural proteins NS3 and NS5
10) Also use RT-PCR and branched chain hybridization of DNA to det viral load

Hepatitis E – Calicivirus

1) Feces contaminated water borne NANB hepatitis.
2) No chronic infection, distinct from HAV
3) 20% fatality in pregnant women

IX) Orthomyxoviruses - Influenza

General

1) Enveloped (HA and NA glycoproteins), segmented, neg sense ssRNA
2) Replicates in nucleas, helical nucleocapsid
3) Steals caps from host mRNA for viral mRNA
4) Local infection of resp tract with constitutional sxs
5) Spreads easily
6) Antigenic varients in host are selected to avoid circ Igs, therefore annual revision of vaccine
7) Antigenic shift (reassortment with mult genomes present in same host) and drift (mutation) in HA and NA antigens. Shift causes epidemics
8) Anitvirals target M2 protein (inhibit virus uncoating) and inhibit neuraminidase

Clinical

1) Protracted illness, respiratory and systemic symptoms
2) Short incubation, no viremia, replication in resp epi
3) Interferon and cytokines cause systemic symptoms
4) Igs and T-cells attack virus, immunity from IgA in resp tract
5) Antigenic variants may be selected in mild secondary infections
6) Complicated by bacterial pneumonia, encephalitis, pericarditis, Reye's syndrome
7) Young kids and elderly at highest risk
8) Influenza A – zoonotic, causes epidemics, **only one that has Antigenic shift**, Influ B and C only human hosts
9) Grow virus in eggs or cell cultures, diag via PCR
10) Original antigenic sin – Immune response to first infection dominates immune response in subsequent infection of different flu virus, therefore increase vaccine difficulty

Viral Proteins

1) HA – hemagglutinin – vaccine target, 95% of outer spikes, binds to sialic acid, host range and spread
2) NA – neuraminidase – vaccine/drug target – 5% of outer spikes, cleave sialic acid from HA, NA and surface of host cell, therefore promotes virus release from cells
3) M1 – Matrix protein - binds RNP complex for xport to cytoplasm
4) M2 – forms Ion channel – drug target (amantadine/rimantadine), lowers pH in virus particle, removes M1 from RNP complex
5) NP – Nucleocapsid protein – protects viral RNA from degradation, forms capsid
6) NS – Non structural protein – NS1/NS2, unknown function
7) PB2/PB1/PA – polymerase components of RNP

Replication

1) Bind sialic acid and endocytosed
2) Low pH in endosome, conform change in HA, viral fusion with endosome membrane
3) Nucleocapsid xport to nucleus
4) Steals caps from host mRNA for viral mRNA
5) Nucleocapsid assembled in nucleus, xport to cytoplasm
6) Virons bud from apical plasma membrane of resp epi cells

7) HA and NA of Influ A have many different variants
8) Defective interfering particles have viral Ags but cannot replicate

Vaccine and Drugs

1) Killed, parenteral, 3 strains (2A's and 1B)
2) Amantadine (24-48hrs after sx) and Rimantidine target M2 ion channel protein that alters pH for viral uncoating and assembly. Both specific for A virus
3) Relenza and Tamiflu are both neuraminidase inhibitors for A and B viruses

X) Viruses of Pediatric Importance - TORCHES

1) Toxoplasm
2) Rubella
3) CMV
4) HSV
5) Enteroviruses
6) HIV
7) Syphilis

XI) Paramyxoviruses

General

1) Large, enveloped, neg sense ssRNA, no segments.
2) Diseases of URT, LRT, measles, mumps and neuro.
3) Most important agents of resp infection in infants and young kids

Structure and Replication

1) NP – nucleocapsid protein
2) M – matrix protein
3) HN – hemagglutinin-neuraminidase glycoprotein, attach to sialic acid receptors
4) H only in measles (no N) , G only in RSV (no HN)
5) F – fusion glycoprotein, cleaved to active form by cellular proteases
6) L – RNA polymerase
7) P – phosphorylated protein for polymerase activity
8) Binds to sialic acid containing receptors
9) Envelope fuses with cell mem at neutral or alkaline pH
10) Transcription on cyto produces full pos sense genomic template
11) Full length neg sense genomic RNA from pos sense template
12) Nucleocapsids assemble in cyto and migrate to cell membrane
13) HN, F and M on formed envelope
14) Large syncytium forms in infected cells with F0 cleavage
15) Most do not kill cell – persistent infections with mutants, altered virulence and tropism

Detection and Patho for Resp Infections (Parainfluenza 1-4 and RSV)

1) Isolated from resp secretions, CSF or urine
2) RBCs stick to infected cells- heme absorption, cell fusion, IF or RT-PCR

3) Specific Ig detection methods
4) Local infections of resp tract, no systemic disease
5) RSV and PIV3 (Para 3)– 30% of severe resp dx in infants and kids
6) Reinfection common, no vaccines, natural infection is not protective
7) 30% mortality in BM xplant

Systemic Infections

1) Mumps
    a. Long incubation (3 wks)
    b. Initial in resp tract then to many epithelial cells
    c. 50% subclinical
    d. Complications – meningitis, encephalitis, nerve deafness, epidiymoorchitis
    e. Life long immunity with infection
    f. Maternal Igs to baby
    g. Live attenuated vaccine with measles and rubella
2) Measles
    a. Highly infectious febrile exanthems (rash), viremia, mult organs
    b. Long incubation (2 wks)
    c. Start respiratory and spreads all over
    d. Symptoms from immune response, reduced CMI- no rash
    e. White pustules inside cheek prelude to rash
    f. Fading or rash marks virus clearance
    g. Complications – common, encephalomyelitis, seizures, mental retardation, bacterial super infection, otitus media and pneumonia. Replicates in LN – pos PPD
    h. Causes immune suppression – unknown mechanism
    i. Neurocomplications – ADEM (PIE) days later, MIBE months later, SSPE years later
    j. One serotype WW, CMI required to clear virus, Breast-feeding protects
    k. Live attenuated vaccine – must give to HIV+ kids w/o AIDS
    l. Boosters recommended before college, boot camp
    m. Passive immunization protection
    n. Subacute Sclerosing Panencephalitis – 1 in 300,000 cases, slow, progressive, fatal, CNS

3) RSV – Resp syncytial virus
    a. Genus – Pneumovirus, no HA or NA attachment proteins
    b. Contains fusion glycoprotein
    c. Most important cause of LRT infection in young kids, resembles common cold in most
    d. No vaccine, replication only in resp epi cells
    e. Immunity is not long lasting
    f. RespiGam – polyclonal Ig drug
    g. Synagis – monoclonal Ig against F protein for high risk pediatric pts

XII) Rubella - Togavirus

General

1) Small, enveloped, pos sense ssRNA, no segmentation
2) Causes congenital rubella syndrome – attacks fetus
3) Only natural reservoir is humans
4) Live attenuated vaccine
5) Persists in host for many years w/o sxs

Properties

1) Viral envelope (toga) from host plasma membrane with E1 and E2 glycoproteins
2) E1/E2 form heterodimer in a trimer spike
3) Enters via endocytic path and need low pH for fusion and release of genome into cytoplasm
4) Pos sense RNA provides message for viral polyprotein precursor for replication required proteins
5) Polymerase transcribes genome into a neg sense RNA template then make full pos sense mRNA

Clinical

1) Mild in kids or adults
2) Maculopapular rash (colored, elevated patch of skin) 95% of cases, enlaged LNs, low fever, sore throat, conjunctivitis and arthralgia
3) Spread by aerosolation, nasopharyngeal and URT initial virus entry
4) Spreads via LNs, painful in adults but not kids, start of viremia, fever and rash later
5) 7-9 day incubation, rash at 16-21 days – IgM at same time against E1
6) Host infectious with virus infection in pharynx
7) Mom and fetus cannot clear virus even though IgG (mom) and IgM (fetus) is present
8) Natural immunity lasts for years
9) Immuno deficient mom may have infected placenta and spread virus to fetus
10) Highly teratogenic – deafness, blindness, heart and brain defects in 15-30% during 1st trimester
11) Often confused with measles, scarlet fever, roseola, and other rash producing viruses
12) Can only diag with seroconversion or virus isolation
13) HAI – humagglutination inhibition is the gold standard for diagnosis
14) Rubella has ags that cause RBC to attach
15) Mild symptoms in vaccinated women (10-40%), but does not have teratogenic ability like wild type

XIII) Picornaviruses

General

1) Common colds (rhinovirus), polio, hepatitis A, foot and mouth disease
2) Very stabe, water borne
3) Most enteroviruses cause subclinical infections
4) 100 types of Rhinovirus cause common cold
5) Enteroviruses
    a. Alimentary tract
    b. Poliovirus – first vaccine, first crystallized virus, first growth in tissue culture
    c. Coxsackievirus Groups A and B

    d. Echovirus (enteric cytopathic human orphan)
    e. All acid stable, pH 3-5, allows survival thru GI tract and fecal-oral spread
6) Rhinovirus
    a. Nasopharyngeal region
    b. Common cold in adults and kids
    c. 100 serotypes
    d. Acid labile, pH 6
    e. Spread by self inoculation
7) Hepatovirus
    a. Hepatitis A
8) Apthovirus
    a. Foot and mouth disease
    b. Infect cloven footed animals, rarely humans
    c. Very contagious
9) Cardiovirus
    a. Strain of encephalomyocarditis virus
    b. Usually murine but can infect humans
    c. Acid stable

Properties and Replication

1) pos sense ssRNA, poly A 3' tail (removal decrease infectity)
2) RNA is infectious
3) Vpg protein at 5' end for packaging and initial RNA syn
4) Genome – single open reading frame from long polyprotein precursor (cleaved early)
5) Coding regions P1, P2 and P3, separated by proteinases 2A and 3C
6) VP 1,2,3 outer epitopes, VP1 major attachment protein
7) VP 4 internal to capsid
8) Cleavage of VP0 yields VP2 and VP4, required for infection
9) 5-fold axis of symmetry with surrounding canyon (receptor binding site), virus drawn into cell
10) Receptors
    a. Polio – polio virus receptor
    b. Rhino and Coxsackie use ICAM-1 (natural ligand is LFA-1)
    c. Echo – VLA-2
11) Receptor canyon binding model (PVR based)
    a. Binding site located in canyon on capsid surface
    b. Neutralizing Ig cannot reach, instead block entry of cellular receptor into canyon
    c. Receptor-canyon interaction is a target for rationally designed antivirals
12) Virus binds to cellular receptor and genome is uncoated
13) VPg removed from RNA and translated
14) Polyprotein cleaved for individual viral proteins
15) Pos sense RNA copied to form full length neg sense RNA and copied again to form pos sense RNA for packaging with VP 0,1,3
16) 5 pentamers assemble for form immature capsid
17) New virus particles released by lysis (5-10 hours)
18) CPE – rapid decline of host cell metabolism, margination of cell chromatin, vesicles spread thru cyto

Poliovirus

1) Entry through mouth
2) 7-14 day incubation
3) Replication in gut, viremia, replication in RES and target organs (brain, SC, meninges)
4) Most cases subclincal
5) Serum Igs prevent viremia and CNS invasion
6) Secretory Ig required to prevent initial local infection
7) Paralysis (1% of cases)
8) Diag via serology, virus isolation, RT-PCR and DNA hybridization
9) Salk vaccine (IPV) inactivated, 1st to be licensed, multiple doses, induces only serum Ig's
10) Sabin vaccine (OPV) live attenuated, all 3 serotypes, type 3 can revert to wild type, induces serum Ig's, and local GI and nasal Ig's.
11) VAPP can occur in immune surpressed 1 per 2.4 million doses
12) US – IPV only, 4 doses, OPV only in unusual circumstances

Coxsackievirus – Spring/Fall high incidence

1) Group A
    a. Herpangina – discrete vesicles on anterior tonsillar pillars, short fever and sore throat
    b. Hand foot and mouth – vesicular herptiform rash
    c. Acute hemorrhagic conjunctivitis
2) Group B
    a. Mild or fatal enceph
    b. Cardiomyopathy and pericadiopathy
    c. Aseptic meningitis
    d. Pleurodynia – fever and chest pain

Enteroviruses – Spring/Fall high incidence

1) Mild fever, cold, diarrhea
2) **Type 70 – agent of hemorrhagic conjunctivitis**
3) **Coxsack A and B and Echoviruses – most common cause of viral meningitis, not as serious as bacteria causes, but highly contagious and often with rashes**
4) Entero and Coxsack assos with paralysis
5) **Type 71 – isolated from throat, rectum, stools, CSF from fatal and non-fatal cases of serious CNS complications**

XIV) Antiviral Drugs

Difficult Development

1) Inability to distinguish viral replication mechanisms from host mechanisms
2) Difficult to design and test in vitro studies
3) Screening – Random chemicals of the shelf – low yield of hits
4) Rational Design – Must know structure and mechanisms to develop inhibitory control
5) Most development somewhere in between pure screening and rational design
    a. Ethnobotany
    b. Select active but toxic agent and attempt to remove toxicity
    c. Pick DNA polymerases and test with cancer pts with minimal toxicity

    d. Most from screening variations and most are toxic
6) In vitro success usually does not show in vivo success

Acyclovir

1) Very effective against HSV, but less against VZV
2) Highly selective and safe, oral administer
3) Cyclic guanosine derivative
4) Inhibits viral DNA synthesis via chain termination
5) Can only be monophospho by viral tk, not cellular, therefore can only become active in virally infected cells
6) High IV dose to neonatal HSV, HSV enceph, dissem infections, immunocompromised kids w/VZV
7) Low oral dose to suppress recurring genital HSV, prophylaxis for oral HSV
8) High oral dose to chicken pox and shingles
9) Drug resistance with immune compromised
10) Gangiclovir – CMV – not the same tk as HSV, prevent untreated blindness, severe CMV w/AIDS
11) Famciclovir/Valacyclovir – New oral for HSV, activated in GI, less dosing, higher serum levels
12) Vidarabine – purine nucleoside analog, chain termination, topical HSV keratitis
13) Idoxuridine/Trifluridine – pyrimadine nucleoside analogs, ophthalmic topical HSV keratitis
14) Cidofovir – New, first nucleotide analogue, CMV retinitis, no viral activation thus can act to protect uninfected cells, long intracellular half life

Foscarnet – PFA

1) Inhibits DNA polymerase
2) Blocks pyrophosphate binding site on polymerase
3) Life-threatening only b/c of kidney toxicity
4) Drug resistance

Rimantadine

1) Inhibits transmembrane ion channels formed by viral M2 protein
2) Prevents M1 xport to nucleas
3) **Prophylaxis against influenza A but not B**
4) Drug resistance from change in M2

Zanamivir

1) Inhalable antiviral drug
2) Inhibits neuraminidase in influenza type A and B
3) Inhibits viral spread
4) Must take between 30-48 hrs of sxs to max benefit
5) Neuraminidase cleaves sialic acid residues and allow virus to spread
6) Tamiflu – oral – common forms of influenza, stops spread of virus

Ribavirin

1) Nucleoside analog
2) Only drug to treat RSV pneumonia
3) Value controversial
4) Combo therapy for Hep C with injected interferon alpha-2b

Interferon

1) Inhibition of viral RNA via protein kinase that inhibits translation initiation complex and activation of an endonuclease that degrades viral RNA
2) Active against HCV, HBV and HPV, only treatment for chronic HBV and HCV
3) **No drug resistance**

Zidovudine/Azidothymidine (AZT)

1) Analog of thrymidine
2) Inhibits viral DNA synthesis
3) Incorporated in viral DNA and causes chain termination
4) Very active against HIV
5) Resistance w/in 6 months
6) Other anti-HIV - nucleoside RT inhibitors, non-nucleoside RT inhibitors and protease inhibitors
7) Fusion inhibitors for HIV-1 – targets membrane fusion step mediated by gp120 and gp41, never use alone because of resistance

Others

1) Pleconaril – pill against picornoviruses (rhino and entero)
2) Respigam – polyclonal - HSV
3) Synagis – monoclonal, better than respigam against HSV
4) Cytogam – passive immunity against CMV, prophylaxis for xplant pts

Resistance and other points

1) Drug resistance mostly in immuno compromised pts, exception is rimantadine
2) Non-compliance with AIDS increases drug resistance, pre-existing mutants are selected
3) Drug combos usually work better than solos
4) Treatment of acute or recurrent genital HSV will not prevent recurrences
5) Treatment for HIV will not remove virus from host
6) Toxicity is more likely if drug cannot be removed readily
7) Oral drugs is almost always better than IV drugs
8) New protease inhibitors of HIV cannot reach CSF

XV) Retroviruses

General

1) Useful as vectors for gene delivery in vivo and in vitro
2) Enveloped RNA virus that produces a DNA provirus via RT
3) Provirus integrates into host chromosome and stay for life in infected cells
4) Oncovirus (HTLV), Lentivirus (HIV) and spumavirus
5) Three cancer mechanism – 1st two animals only, 3rd humans
    a. Acute transforming types transduce oncogenes into genome of host cell
    b. Non-acute transforming types integrate IVO cellular proto-oncogenes and augment their expression
    c. HTLV-1 syn trans-activating factors that de-reg gene expression causing abnormal cell proliferation (trans-activation)

6) HTLV-1 and 2 cause Adult T-cell leukemia via expression of host GF and receptor
7) Lentiviruses (slow) encode additional reg proteins that assist viral infection and replication

Structure and Replication

1) Envelope proteins – SU (surf) and TM (transmembrane)
2) Core proteins – NC (nucleocapsid), CA (capsid) and MA (matrix)
3) Enzymes – RT (reverse transcriptase), IN (integrase), PR (protease)
4) Genome – two ssRNA subunits encode gag, pol and env
5) Transcribed into dsDNA by RT after uncoating
6) Integrates into host DNA by integrase and becomes a provirus, therefore immune sys can never eliminate the virus without killing the cell
7) Provirus transcribed into viral RNA and mRNA by host RNA polymerase II
8) Gag (group assos antigen) processed into MA, CA, NC and sometimes PR – assembly and packaging of virus
9) Pol (polymerase) processed into RT and IN – principle replication enz and integrator into host DNA
10) Env (envelope) processed into SU and TM – mediate attachment and fusion with cell plasma mem
11) SU and TM define virus tropism
12) First phase – entry and integration into host DNA
13) Second phase – Viral mRNA is transcribed and used to make viral proteins or genomic RNA for virus assembly
14) LTR – long terminal repeats – identical regions on each end of proviral DNA contain potent promoters and enhancers for gene expression and replication

Retroviral Oncogenesis and Gene Therapy

1) Viral genome into host DNA disrupts genes, usually inactivated but can be hyper expressed by LTR
2) Non-acute oncogenic retroviruses - naturally occurring cancer viruses, activation of host proto-oncs, cis-activation by LTR
3) Acute oncogenic retroviruses – carry mutated versions of the cellular proto-oncs and insert them into the host DNA. Cause poly clonal tumors after short latency. No human forms
4) Endogenous retroviruses – incorporated into germ cells and xmit to offspring, most defective
5) Retrotransposons – Endogenous retroviral DNA that can be transposed into other parts of the genome
6) Retroviral vector with two LTRs and w/o gag, pol or env. Most require cell division for integration, but HIV can infect non-dividing cells such as neurons

Retroviral Diseases

1) HTLV-1
    a. Adult T-cell leukemia and tropical spastic paraparesis
    b. Transfer via infected bodily fluids
    c. Must have accessory genes tax (cytokine activation) and rex for replication
    d. ATL – monoclonal, CD4+, infection early, decades to develop, 1% of infected have dx
    e. Tax protein activates viral gene expression and signal paths in T-cells
    f. No treatment

2) HAM/TSP
    a. 20% risk with HTLV-1 infection

b. Uncoordinated motor control, demyelination of pyramidal tracts
c. Infection from blood, rapid onset
d. Tropical spastic paraparesis -weakness, spasticity and peripheral sensory loss
e. No treatment

3) HTLV-II
   a. 65% similarity with HTLV-1
   b. Similar transmission, higher with IV drug users
   c. Assos with T-cell hairy cell leukemia
   d. Treat with interferon-alpha

4) HIV I and II
   a. Infected bodily fluids, very fragile virus
   b. HIV-1 – WW, HIV-2 – more limited
   c. Infection of replication of monocytes and macrophages and spread to all tissues including brain and CNS
   d. Macrophage tropism for initial infection, T-cell tropic during late stage
   e. Macro tropic use CCR5 as corecptor for entry, T-cell tropic use CXCR4
   f. No true latency, continuous infection and destruction of CD4+ T-cells
   g. New HIV variants continually arise b/c of high replication rate and error-prone RT, high selective pressure from immune system cause high gp120 changes to avoid immune system. Alterations in env and pol from host selective pressure and drug therapy.
   h. Continuous and highly productive replication of HIV occurs in all infected people
   i. Billions of cells are created and destroyed in one day
   j. Drugs target RT and proteases
   k. Individual tested for HIV first via ELISA then with Western blot to confirm.
   l. Viral envelope proteins gp120 (attachment) and gp41 (fusion)
   m. Complex retrovirus with 6 accessory genes
   n. P24- major capsid protein, p17 – matrix protein, 2 copies of plus sense RNA and 3 viral enzs RT, IN and protease
   o. The env gene contains the determinant for tropism, M-cell, T-cell or Dual
   p. Viral RT converts viral RNA into dsDNA then goes to nucleus and integrates with host DNA to make a provirus DNA
   q. Seroconversion in 8-12 weeks, virus is throughout lymphoid system, 5-10 times than blood
   r. Marker and time to detect
      i. RNA – 11 days
      ii. DNA – 16 days
      iii. P24 ag – 16 days
      iv. Ig – 22 days

XVI) Arboviruses

General

1) Arthropod-borne virus, reservoir is usually animals, humans are dead-end hosts
   a. West Nile
   b. Western, Eastern, Venezuelan equine encephalitis

    c. Jungle yellow fever
2) Can be human-insect-human
    a. Dengue
    b. Urban yellow fever
3) Insect can be a reservoir if transovarial xmission occurs
4) Flu-like sxs - Non-specific fever, rash, aches, chills
5) Encephalitis – VEE/EEE/WEE, West Nile, Saint Louis, Japanese
6) HF – Yellow fever, dengue, Crimean-Congo
    a. Severe multi-system syndromes
    b. Vascular system is damaged
    c. Impaired regulation
    d. Fever, fatigue, dizziness, muscle aches, loss of strength, exhaustion
    e. Pts rarely die from blood loss
7) Diag usually via serology, poss culture or direct ag test or PCR
8) Emerging dxs because – animal/human travel, irrigation, development, new migration routes

West Nile

1) Flavivirus, pos sense RNA
2) Carried by birds
3) 20% mild illness (WN fever)
4) Severe infection 1 in 150 develop neuro dx – mental status, ataxia, seizures, myelitis, optic neuritis
5) Be suspicious in pts with unexplained enceph or mening in summer/early fall
6) Detect via IgM to WNF in serum or CSF, supportive treatment

Japanese Enceph

1) Flavivirus, China, India, Asia
2) Most subclinical, 1/300 develop severe enceph
3) Diag via serology
4) Killed vaccine available
5) Vector – Culex mosquito

Yellow Fever

1) Flavivirus – W. Africa and S. America
2) Jungle YF – Natural reservoir for disease, primates and forest mosquitos
3) Urban YF – Humans and Aedes aegypti
4) Chills, fever, headache, GI bleed (black vomit), liver, 50% die
5) Diag via serology
6) Live attenuated vaccine

Dengue

1) Biggest arbovirus problem today – 2 million cases/yr
2) 4 Serotypes xmitted by Aedes mosquito
3) Human infection from human-mosquito-human xmission
4) 1st time – flu-like illness
5) Additional infections with diff serotypes – escalating sxs
6) Dengue HF or Dengue shock syndrome – subsequent infections – immuno-path mechanism

7) Diag via serology
8) No cross protection, old Ig's enhance new infection

Togaviruses

1) Vector is mosquito, equine enceph viruses
2) EEE – rarest type, 1 in 23 neuro effects, 50% deaths in all age groups
3) WEE – neuro sxs 1 in 1000 for adults, 1 in 25 for infants, 60% of survivors perm neuro effects
4) VEE – Rodents and mosquitos (not birds), neuro effects less common and severe than EEE/WEE

Bunyaviruses – insect borne

1) Three pieces of genome – poss reassortment
2) La Crosse – most important cause of kid arbovirus enceph in US
3) Localized in Midwest states, most infections subclinical

Hantavirus – rodent borne Bunyavirus

1) Inhale rodent excrement or by direct skin contact
2) HF with Renal Syndrome – HFRS
3) Fever, headache, hemorrhage and acute renal failure
4) Sin Nombre in four corners area of US – Hantavirus pulmonary syndrome
5) Clinical
    a. Damage to caps and small vessel walls – vasodilation and congestion
    b. Phases – Fever, Hypotensive, Oliguric, Diuretic, Convalescent
    c. Long time to improve and recover
6) HPS – 50% mortality in N. and S. America – cap damage in lungs vice kidney
7) Diag via serology for HVD and HPS, direct ag test, possible isolation
8) Treatment mostly supportive, poss ribavirin use in HVD
9) Rodent control

Colorado Tick Fever Virus

1) Rodent borne, tick vector
2) No envelope, dsRNA, 12 segments
3) Wood tick, humans spring and fall
4) West and NW US, W. Canada
5) Infects early RBCs and persists
6) Serious hemorrhagic dx of the vascular epithelium
7) IF for ag on blood smear
8) Usually mild or subclinical dx – fever, chills, headache, myalgia, lethargy

XVII) Viral Agent of Bioterrorism

CDC Listing

1) Cat A – Smallpox- Variola Major, VHFs
2) Cat B – Viral enceph
3) Cat C – Nipah and hantaviruses

VHF

1) Five distinct families
    a. Arena – Lassa Fever, S. Americans VHFs, LCM
    b. Bunya – CCHF, HPS, HFRS, rift valley
    c. Filo – Ebola, Marburg
    d. Flavi – Omsk, Kyasanur Forest
    e. Paramyxo – Hendra, Nipah enceph
2) Fever, headache, malaise, dizziness, myalgias, nausea, vomit
3) Positive tourniquet test
4) 10-90% mortality, virus specific
5) Person to person xmission for Ebola, Marburg, Lassa and Crimean-Congo
6) Supportive care – no antiplatet drugs or IM injections, possible Ribavirin
7) Body fluids contaminated with virus

Filoviruses – Ebola and Marburg

1) Enveloped, ssRNA neg sense
2) 4 subtypes – 3 cause dx in humans, Ebola-Reston only non-human primates
3) Unknown natural reservoir
4) Infections are acute, w/o a carrier state
5) Direct contact with blood and other fluids
6) Early red eyes and skin rash, only supportive treatment

Arenaviruses – LCM, Lassa and S. American HFs

1) Rodent-borne – contact with exreta via aerosol
2) Uniques ambisense RNA, pos and neg strands together
3) Lymphocytic Choriomeningitis (LCM) – aseptic meningitis or enceph
    a. Usually mild or asx
    b. Under-recog complication of pregnancy
    c. House mouse reservoir
    d. Biphasic fever after 8-13 days, 2^{nd} phase meningitis
    e. Usually not fatal 1%
4) Lassa Fever
    a. W. Africa
    b. Human to human xmission
    c. 80% asx or mild, but other 20% severe multi-sys dx
    d. 50% case rate mortality
    e. Rodent reservoir
    f. Fever, sore throat, back pain, facial swelling, mucosal bleeding
    g. Deaths rate very high for women in 3^{rd} trimester
    h. Deafness most common complication
    i. Ribavirin can work if given early
    j. ELISA for IgM and IgG and Lassa ag

Paramyxoviruses

1) Hendra virus – horses and humans
2) Nipah virus
    a. Enceph

b. Pigs in SE Asia
c. 40% case fatality
d. Person to person, bat reservoir
e. Cat C by CDC

Smallpox

1) All pox viruses cause skin lesions
2) Big virus – can be seen on LM
3) Complex – not icosahedral or helical, dsDNA, very stable
4) Only DNA virus that replicates in cytoplasm
5) Replication
    a. Uncoats in 2 stages – virus core into cyto and DNA from core
    b. Viral RNA makes viral mRNA
    c. Viral DNA polymerase and thymidine kinase to syn new DNA
    d. Rifampin blocks assembly of viral envelope
    e. Methisazone blocks last protein syn and assembly
6) 30% mortality w/o vaccination
7) Rash more on face and extremities and less on trunk, contrast with chicken pox
8) Lesions all at same stage of development
9) Diag via inclusions from lesions scrape
10) Person to person contact, does not survive on clothing, no non-human reservoir, no carriers
11) Vaccination
    a. Very rare adverse rxn to vaccine, improper immune response, systemic infection
    b. Eczema vaccinatum – skin lesions over much of body, treat with VIG
    c. Postvaccination enceph – 1 in 200,000, no treatment
    d. Do not use on pregnant women or immune suppressed pts
    e. VIG – can only use for adverse rxns not natural disease
12) Eradication
    a. No animal reservoir
    b. No recurrent infections
    c. One or few stable serotypes
    d. Easy vaccine
    e. No subclinical infections

XVIII) Bunya and Flavi Viruses

Dengue Fever

1) DHF mortality up to 30%, mosquito vector
2) Often unspecified fever in military troops
3) Most important Arbovirus WW
4) Can be reinfected – immune response worse for subsequent infections
5) Historically in SE Asia
6) Only humans
7) DF – self limited, abrupt onset, headache, orbital pain, bone pain, anorexia
8) DHF – DF with hemorrhagic sxs and plasma leakage into lungs
9) Epidemics in Saipan, Australia, Hawaii, New Hebrides, Vietnam, Somalia, Haiti

Japanese Encephalitis

1) Okinawa 1945, China, Philippines 1945, India, Nepal, SE Asia, Chiang Mai Valley
2) Biggest enceph problem b/c of at risk population
3) Mosquito vector
4) Zoonotic in pigs and waterfowl
5) Mild fever, acute meningoencephalitis, depressed consciousness, motor impairment
6) 50% neuro sequelae, 25% die

Rift Valley Fever

1) Threat to forces in Middle East
2) Found mostly in sub-Sahara Africa
3) Human infections from contact with infected animals
4) Undifferentiated fever, autoimmune retinitis, myalgia, lower back pain, eye pain
5) Frequent abortion and neonatal death in livestock, ataxia, mucopurulent from nose and stools

XIX) Slow and Unusual Viral Infections

Curetzfeld Jacob Disease/Kuru group – Transmissible Spongiform Enceph, Infectious Amyloidoses

1) Spongiform encephalopathy
2) Animal dxs
    a. Scrapie – chronic fatal ataxia and pruritis
    b. Bovine SE – Mad cow disease
3) Human dxs
    a. Kuru – Human SE – cerebellar ataxia and shivering – eat the dead in New Guinea, 30 year incubation
    b. CJ Disease – SE, sporatic, dementia, world wide, 5-10% familiar, amyloid deposits in brain
4) Filterable agent, highly resistant to chemicals/irradiation, amyloid protein is protease resistant (PrP)
5) Prion hypothesis – PrP is infectious agent.
6) New variant CJD – high freq of amyloid plaque formation in the young, EEG sxs. In mice death like BSE, not CJD

XX) Fungus General

1) Eukaryotic, Aerobic, Saprophytic (nourished from products of organic breakdown and decay)
2) Cells walls made from protein and carbs
3) Cell membrane with phospholipids and ergosterols
4) Capsules
5) Thermal dimorphism – different forms at different temperatures
6) 5-10 times larger than bacteria
7) Yeast – round buggers
8) Hyphae – septate or nonseptate
9) Pseudohyphae (Candida)
10) Mostly haploid state
11) Classifications
    a. Ascomycetes – Aspergillus, Histoplasma, Blastomyces, Dermatophytes

b. Basidiomycetes – Cryptococcus, Mushrooms
c. Zygomycetes – Mucor, Rhizopus
d. Deuteromycetes (Fungi Imperfecti) – Sporothrix, Coccidioides, Candida

12) Transmission
a. Respiratory inhalation (systemic) – most common
b. Cutaneous inoculation (sporotrichosis)
c. Systemic from normal flora – opportunistic (Candida)
d. Contact with infected host (rare human to human) – dermatophytoses

13) CMI most important to fight infection (esp phagos)– Diabetes, AIDS and immune suppressed pts at risk

14) Diagnosis
a. Gram stain – not specific for fungus
b. India Ink – use on CSF, shows capsule, need many orgs
c. KOH wet prep on skin scrapings – digest away host tissue
d. Calcifluor white – KOH – shows cell wall, binds chitin, need UV light
e. Formalin fixed tissue
i. H&E stain
ii. PAS – periodic acid schiff
iii. Silver stain – small # of bugs, shows segmentation
iv. Mucicarmine – shows polysaccs in cryptococcus

15) Histological response
a. Acute pyogenic abscess – Candida
b. Chronic granuloma – Histoplasma
c. Chronic, local dermal inflamm – Dermatophytes
d. Mixed pyogenic and granuloma – Blastomyces
e. BV invasion w/thrombosis – Mucor and Aspergillus
f. Allergic hypersensitivity, no invasion – bronchopulm aspergillosis

16) Culture with Sabouraud agar w/xbios – ID from temp of growth, rate, **morphology (most common),** bio reactions, spore pattern and selective media. Cycloheximide – stops protein syn in some mycoses

17) Serology – Usually poor, but
a. Cryptococcal ag via latex agglutination in CSF and blood
b. Histoplasma capsulatum poly sac ag (HPA) in urine
c. Assay for Aspergillus
d. Coccidioides – early IgM and CSF IgG

18) Drugs
a. Polyenes (Ampho B) – act on cell membranes – binds to ergosterol, cause leakage, **fungicidal, nephotoxic, acts on Candida, Crypto, Asper, Histo, Blasto, Cocci**
b. Azoles (Fluconazole et al.) – act on cell membranes – prevents ergosterol syn, fungistatic, acts on Candida, Crypto, Trichsporonosis, Dermatophytes
c. Echinocandins (Caspofungin) - act on cell wall
d. Nucleoside derivatives (5-flurocytosine) – inhibits RNA and DNA synthesis, acts on yeast, use with Ampho B on Crypto and Candida, narrow spectrum, resistance if used alone
e. Azole (Itraconazole) – Prevents ergosterol syn, acts on systemic mycoses, yeasts, Dermatophytes
f. Candcidas – inhibits beta glucan syn, static and cidal, acts on Asper, Candida, **but not Crypto**

19) Early Diagnosis
a. Due to immunosuppression typical sxs are absent
b. Few unique clinical sxs

c. Blood and sputum usually negative
d. Invasive procedures required to diagnose

XXI) Cutaneous Fungal Infections

Dermatophytoses – Epidermophyton, Microsporum, Trichophyton

1) Common in animals, few in humans
2) Invade only nonliving keratinized structures
3) Stratum corneum of skin, hair and nails
4) Secondary infection with bacteria common
5) Low inflammatory response assos with chronic low grade infections
6) Manifestations designated by location of infection (i.e. Tinea capitis)
7) Bugs are active on the leading edge of rash
8) Tinea unguium – under nails, must take oral anti-fungal to cure
9) Treatment via topicals, systemic, Azoles (ketoconazole, itraconazole)

Other Superficials

1) Malassezia furfur – lipid dependant yeast – pityriasis versicolor
2) Tinea nigra – Black patches – Exophiala werneckii – black pigment from bug
3) Piedra – grows on hair – white – trichosporon beigelii – opportunistic

XXII) Subcutaneous Fungal Infections

Sporotrichosis

1) Sprorothrix schenkii – thermal dimorphism, black pigment, easy to grow
2) High assos with wood or plant products
3) Direct inoculation
4) Pyogenic and progresses via lymph nodes
5) Looks like Cutaneous leishminiasis
6) Yeasts and moulds

Chromoblastomycosis (muriform bodies (copper penny)) & **Phaeohyphomycosis** (hyphae in tissue)

1) All make brown pigment
2) Usually tropical, direct inoculation from soil
3) Slow progression and not invasive
4) Pyogenic or pyogranuloma

Lobomycosis (not in US)

1) Chronic Cutaneous or subcutaneous infection
2) Localized, forms keloids, verrucoid to nodular lesions, crusty plaques and tumors
3) Lacazia loboi – has never been isolated in vitro, can be seen on LM w/silver stain
4) Latin America
5) Subepidermal granulomas, chain of globose cells, each connected via a narrow neck
6) No drugs, only surgery
7) Diag via LM mounted in 10% KOH – look for globose cells

Mycetoma

1) Invade muscle and bone
2) Tropical and subtropical, direct inoculation into skin
3) Pyogenic, granule formation, invasive
4) Actions similar to bacteria
5) Single little spores on hyphae
6) Pseudoallescheria boydii (colony)
7) Can only amputate, no drugs, slow progression
8) **Opportunistic in AIDS, immunosuppressed, xplant, CNS mold disease**

XXIII) Systemic Mycoses

Histoplasmosis – Histoplasma capsulatum

1) **Mostly Lungs** – also spleen, liver, bone marrow (RES)
2) Forms Granulomas
3) Dimorphic with temperature
4) Produces characteristic tuberculate marcrocondia
5) Grows slowly and grows on cycloheximide
6) Bird/Bat droppings, inhalation
7) Sx very similar to TB
8) Persists intracellular as yeast phase
9) Makes big and small spores
10) CMI required for protection – can reactivate
11) Pneumonia, histoplamoma (tumor), disseminated
12) Most cases mild or subclinical
13) Diag best via biopsy and special stains
14) HIV may require life-long suppression therapy
15) Treat with Itraconazole (moderate), Ampho B (serious)

Blastomycosis – Blastomyces dermatitidis

1) **Mostly Lungs** – also skin, bone
2) Forms Pyogranulomas and microabscesses
3) Dimorphic with temperature
4) Forms characteristic thick walled broad based budding yeast cells
5) Grows slowly and grows on cycloheximide
6) Important disease in dogs
7) Most cases subclinical or undiagnosed
8) Pneumonia, blastomycoma, osteomyelitis, Cutaneous (after dissemination)
9) Diag best via microscopy exam of biopsy
10) Only makes small spores
11) Treat with Itraconazole (moderate), Ampho B (serious)

Coccidioidomycosis – Coccidioides immitis

1) **Mostly Lungs** – also bone and CNS
2) Forms pyogranulomas
3) Dimorphic – mold (in vitro), spherule (in vivo)

4) **Rapid growth at 37C as mold** and grows on cycloheximide
5) Often infects lab personnel
6) **Forms arthrocondia – special spore**
7) Restricted to semi-arid regions of N and S America
8) Saprobic and Parasitic life cycles
9) Condia swell and form spherule, spherule forms many endopspores, spherule ruptures and releases condia for inhalation into parasitic host
10) Most cases mild or subclinical
11) Pneumonia, CNS and bone
12) Diag best via LM and biopsy
13) Treat with Itraconazole/Fluconazole (moderate), Ampho B (serious)

Paracoccidioidomycosis – paracoccidioides brasiliensis

1) Dimorphic with temperature
2) **Characteristic multiple budding yeast cells**
3) Chronic mucocutaneous, mucous and skin
4) Limited to tropical and subtropical S. America
5) **Mostly lungs via inhalation** – also dissem in HIV, mucocutaneous ulcers, pneumonia, meningitis
6) Diag best via LM and biopsy
7) Treat with Itraconazole/Fluconazole (moderate), Ampho B (serious)
8) **TMP/SMX suppression in HIV**

XXIV) Opportunistic Fungal Infections

Population at Risk

1) Xplant pts
2) HIV
3) Malignant diseases
4) Congenital immunodeficiency
5) Hospitalized with invasive devices
6) Instances of neutropenia

Candidiasis

1) Most common opportunistic infection
2) Has yeast, hyphae and pseudohyphae all at same time, produce blastocondia
3) Rapid growth
4) Normal flora of GI tract – overgrowth during broad spectrum xbios, cytotoxic drugs
5) Colonizes vascular or urinary catheters
6) Mucosa, Cutaneous, systemic (kidney, urinary, liver, spleen, eye)
7) Chronic mucocutaneous - macro defect, poly's fine therefore not systemic
8) Diag via LM of biopsy and rapid sensitive culture techniques
9) Distinctive chlamydospore
10) Treat with nystatin and ampho B for topical infections
11) Treat with Azoles (some resistance), ampho B and flucytosine (no alone) for systemic infections

Cryptococcosis – Cryptococcus neoformans

1) **Encapsulated budding yeast**
2) **Inhibited by cycloheximide**
3) Grow slower than candida
4) WW – assos with soil and bird feces
5) Primary pulmonary route via inhalation then spread to blood and CNS
6) **Polysac capsule is antiphagocytic**
7) CMI important but still need Igs
8) Most with HIV coinfection
9) Direct LM of fluids with India Ink to see capsule, says nothing if negative but diagnostic if positive
10) Culture and antigen detection is much more sensitive than India ink prep
11) Treat with ampho B and fluconazole, many need life long fluconazole if HIV

Aspergillosis

1) Rapid growth
2) A few of hundreds cause disease
3) Monomorphic molds
4) Hyaline, septate, branching hyphae
5) Diag via condial head on morphology – flowering-like head on hyphae
6) Constant exposure to spores, in soil and plants
7) Request host with neutropenia, rare cases of otitis externa in normal pts
8) Pneumonia, aspergilloma, allergic bronchopulm rxn, disseminated organ involvement
9) Difficult to treat CNS infection
10) Fungus fills in air space secondary to some other disease process
11) Is not isolated from blood
12) Diag via direct LM of biopsy – but presumptive and not definitive, looks like other molds
13) Treat with itraconazole or ampho B or surgery for aspergilloma

Penicillosis

1) Penicillium marneffei
2) Dimorphic – diff from other penicillums
3) Characteristic yeast forms in tissue
4) Assos with bamboo rats in Thailand and SE Asia
5) Assos with AIDS infection
6) Isolated from blood
7) Treat with Azoles, ampho B, long term use of itraconazole with AIDS

Zygomycosis (Mucormycosis)

1) Monomorphic, rapid growth
2) **Isolated from blood**
3) Hyaline, **non-septate branching hyphae**
4) Inhibited by cycloheximide
5) Bread molds – all over the place
6) Usually starts in URT or Lung – inhalation
7) Cleared by normal host
8) Colonizes sinus or lung in compromised host

9) Likes pts with diabetes and ketoacidosis – polys are dysfunctional
10) Invades BVs, blocks and causes infarction
11) Extensive necrosis – pulmonary, renal
12) Rhinocerebral Mucormycosis in Diabetics
13) Diag via LM of biopsy – ribbon-like non-parallel, no septate
14) Treat with ampho B, control diabetes and surgical excision